IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE PROCTER & GAMBLE COMPANY, Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No. 04-940-JJF

PLAINTIFF THE PROCTER & GAMBLE COMPANY'S
PROPOSED FINDINGS OF FACT

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Plaintiff The Procter & Gamble Company ("P&G") sets forth below its proposed findings of fact:

I. INTRODUCTION

1. P&G is a corporation incorporated under the laws of the State of Ohio with its principal place of business at 1 Procter and Gamble Plaza, Cincinnati, Ohio. (Joint Statement of Admitted Facts ("Joint Facts") ¶ 1.)

2. Defendant Teva Pharmaceuticals USA, Inc. ("Teva") is a corporation incorporated under the laws of the State of Delaware, with its principal place of business at 1090 Horsham Road, North Whales, Pennsylvania. (*Id.* ¶ 2.)

3. On December 21, 1984, P&G filed United States patent application Serial No. 684,543 (the "'543 application"). (*Id.* ¶ 5.)

4. On December 6, 1985, P&G filed a continuation-in-part of the '543 application, which was United States patent application Serial No. 806,155 (the "'155 application"). (*Id.* ¶ 9.)

5. The '155 application issued as United States Patent No. 5,583,122 (the "'122 patent") on December 10, 1996. (*Id.* ¶ 13.)

6. JTX 2 is the file history for the '122 patent. (*See* JTX 2.)

7. P&G is the owner of the '122 patent. (*Id.* ¶ 14.)

8. The '122 patent contains 23 claims. (*See* JTX 1.)

9. Claims 4, 16, and 23 pertain to a chemical compound known as 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid, which is also known by the common name risedronate. (*Id.*; Trial Transcript ("Tr.") at 76:12-17 (Lenz Dir.); Tr. at 151:17-18 (Lenz Cross)).

10. Claim 4 claims:

> [a] diphosphonic [and] acid compound, or pharmaceutically-acceptable salt or ester thereof, which is 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid.

(JTX 1).

11. Claim 16 (stated in independent form) claims:

> A pharmaceutical composition comprising:
>
> (a) a geminal diphosphonic acid compound or a pharmaceutically-acceptable salt or ester thereof, at a level providing from 0.001 to 600 milligrams phosphorus in said composition, wherein said compound is 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid; and
>
> (b) a pharmaceutically-acceptable carrier.

(*Id.*)

12. Claim 23 claims:

> A method of treating diseases associated with abnormal calcium and phosphate metabolism, comprising administering to a person in need of such treatment a safe and effective amount of a composition of claim **16**.

(*Id.*)

13. Risedronate is a member of a class of compounds called bisphosphonates. A bisphosphonate is an organophosphorous compound that contains two phosphate groups that are connected to one or more carbon atoms to form a single compound. (Tr. 546:10-14 (McKenna Direct)).

14. Risedronate sodium is sold by P&G under the brand name in the market as Actonel. (Tr. at 74:2-6 (Lenz Dir.)).

15. On March 27, 1998, P&G received FDA approval to market 30 mg tablets of Actonel, for the treatment of Paget's Disease. (Joint Facts, ¶ 15.) P&G received FDA approval to market 5 mg Actonel tablets for the treatment of osteoporosis on April 14,

2000. (*Id.*) P&G received FDA approval to market 35 mg Actonel tablets for the treatment of osteoporosis on May 17, 2002. (*Id.*)

16. The '122 patent covers P&G's 5 mg, 30 mg, and 35 mg Actonel tablets. (Joint Facts, ¶ 16.)

17. By submission dated July 2, 2004, Teva filed Abbreviated New Drug Application ("ANDA") No. 77-132 for approval to market 5 mg, 30 mg, and 35 mg risedronate sodium tablets prior to the expiration of the '122 patent. (Joint Facts, ¶ 17.)

18. For purposes of this litigation, Teva has agreed that its marketing in the United States of its 5 mg, 30 mg, and 35 mg risedronate sodium tablets in accordance with its ANDA would infringe at least claims 4, 16, and 23 of the '122 patent. (*Id.*, ¶ 18.)

II. WITNESSES

A. P&G's Witnesses

1. Dr. John Bilezikian

19. Dr. John Bilezikian is a professor of medicine and pharmacology at the Medical School, College of Physicians and Surgeons, at Columbia University. He is also the Director of the Endocrinology Division and the Director of the Metabolic Bone Disease Group. (Tr. at 335:17-336:1 (Bilezikian Dir.)).

20. Dr. Bilezikian has been a faculty member at Columbia University since 1975. (Tr. at 336:4-5 (Bilezikian Dir.)).

21. Dr. Bilezikian is board certified in internal medicine, endocrinology, and bone metabolism. (Tr. at 337:19-22 (Bilezikian Dir.)).

22. Dr. Bilezikian's sub-specialty within the field of endocrinology is metabolic bone diseases. (Tr. at 337:23-338:3 (Bilezikian Dir.)).

23. Dr. Bilezikian has spent most of his career doing research related to metabolic bone diseases. (Tr. at 342:23-343:2 (Bilezikian Dir.)).

24. Dr. Bilezikian was and is familiar with the state of osteoporosis research in the early and mid-1980s. (Tr. at 365:4-7 (Bilezikian Dir.)).

25. Dr. Bilezikian was involved in some of the earliest studies of bisphosphonates, including etidronate ("EHDP") and clodronate. (Tr. at 365:8-12 (Bilezikian Dir.)).

26. In 1980, Dr. Bilezikian published a paper related to clodronate. (Tr. at 365:12-13 (Bilezikian Dir.)). This was his first published paper. (Id.)

27. Dr. Bilezikian has published approximately 495 articles in the field of metabolic bone diseases. (Tr. at 341:1-6 (Bilezikian Dir.)).

28. Dr. Bilezikian has published between 50 and 75 articles related to bisphosphonates. (Tr. at 341:8-12 (Bilezikian Dir.)).

29. Dr. Bilezikian's research is funded primarily by grants from the National Institutes of Health. His total funding from all pharmaceutical companies, including P&G, is approximately 5% of the funding he has received for research. (Tr. at 347:16-348:2 (Bilezikian Dir.)).

30. Dr. Bilezikian currently spends between 20%-25% of his professional time seeing patients. (Tr. at 345:2-13 (Bilezikian Dir.)).

31. Plaintiff's Trial Exhibit ("PTX") 428 is a copy of Dr. Bilezikian's C.V., which contains an accurate summary of his educational background and professional experience through the end of September 2006. (Tr. at 348:11-18 (Bilezikian Dir.)).

32. Dr. Bilezikian is an expert in the fields of endocrinology, metabolic bone disease, and bone metabolism and has particular experience in the area of osteoporosis and the use of bisphosphonates in its treatment.

2. Dr. James Benedict

33. Dr. James Benedict was a research scientist for P&G from the fall of 1971 until 1986. (Tr. at 412:24-413:8 (Benedict Dir.)).

34. Dr. Benedict has a B.A. in chemistry from Moorhead State University in Minnesota and a Ph.D. in inorganic chemistry from the University of Wisconsin. (Tr. at 412:1-6 (Benedict Dir.)).

35. Dr. Benedict received his Ph.D. in 1971. (Tr. at 412:7-10 (Benedict Dir.)).

36. Upon joining P&G in 1971, Dr. Benedict went to work for the Toilet Goods division (now called Health and Beauty Care), where he worked until approximately 1974. (Tr. at 413:2-5, 414:1-3 (Benedict Dir.)). During that time, he was involved in the development of bisphosphonates for use in oral products, such as dentrifices and mouthwash. (Tr. at 413:9-15 (Benedict Dir.)).

37. In 1974, Dr. Benedict went to work for P&G's corporate research lab, where he remained until he left the company in 1986. (Tr. at 413:22-414:7 (Benedict Dir.)). During that time, Dr. Benedict worked on bisphosphonates for use in treating various diseases, including in particular bone diseases and disorders. (Tr. at 414:8-24 (Benedict Dir.)). Dr. Benedict primarily worked on research concerning bisphosphonates for the treatment of bone diseases for 12 years while he was at P&G. (Tr. at 415:1-6 (Benedict Dir.)).

38. Dr. Benedict's primary responsibilities were to synthesize bisphosphonate compounds and to look at their physical and chemical properties. (Tr. at 415:13-19 (Benedict Dir.)).

39. After Dr. Benedict left P&G, he moved to Colorado and joined a small start-up company looking at bisphosphonates for their anti-mineralization properties in bioprosthetic heart valves. (Tr. at 417:5-13 (Benedict Dir.)).

40. Dr. Benedict has published 25 to 30 articles, abstracts, or chapters in books on the subject of bone diseases and their treatments. (Tr. at 417:14-21 (Benedict Dir.)). He is named as an inventor on 20 issued US patents, with 10 or more related to bone disease, including several that relate to bisphosphonates. (Tr. at 417:22-418:9 (Benedict Dir.)).

41. Dr. Benedict has not received, and will not receive, any royalties from the sale of risedronate. (Tr. at 418:24-419:2 (Benedict Dir.)).

3. Dr. Charles McKenna

42. Dr. Charles McKenna is Professor of Chemistry-[Pharmacology and Pharmaceutical Sciences] (Tr. at 539:2-4), and Director of an Interdisciplinary Program in Drug Discovery at University of Southern California. (Tr. at 538:22-23; 539:7-9 (McKenna Dir.)). He has been a professor there for more than 30 years, and a full professor for the past 17 years. (Tr. at 541:16-21 (McKenna Dir.)).

43. Dr. McKenna received a B.A. in French literature, with a co-major in chemistry, and a minor in Russian, from Oakland University in 1966. (Tr. at 541:24-542:5 (McKenna Dir.)). He obtained a Ph.D. in Chemistry from the University of California in San Diego in 1971. (Tr. at 542:6-8 (McKenna Dir.)). After receiving his Ph.D., Dr. McKenna completed three post-doctoral programs. The first, which lasted

from 1971 to 1972, was in the fields of enzymology and biochemistry at University of California, San Diego with Professor Martin Kamen. (Tr. at 542:11-14 (McKenna Dir.)). The second, as an NIH fellow at Harvard University, which lasted from 1972 to 1973, was in the fields of synthetic chemistry and biochemistry of organophosphorus compounds with Dr. F.H. Westheimer. (Tr. at 542:15-18 (McKenna Dir.)). For the third, he was a NAS Postdoctoral Scholar in the former USSR in 1973. (Tr. at 542:18-22 (McKenna Dir.)).

44. Since joining USC, Dr. McKenna has taught a variety of graduate and undergraduate courses, including chemistry, organic chemistry, advanced organic chemistry, physical organic chemistry, biochemistry, molecular biology, bioorganic chemistry, organic synthesis laboratory, and AIDS and Drug Discovery. (Tr. at 543:14-544:10 (McKenna Dir.)). In addition, he has contributed to two courses in the School of Pharmacy called Drug Development and Drug Discovery Design. (Tr. at 544:10-14 (McKenna Dir.)). Dr. McKenna also has served as a research advisor to more than 50 graduate and post-doctoral students, the majority of which have been focused on the area of organophosphorus chemistry. (Tr. at 544:19-545:6 (McKenna Dir.)).

45. Dr. McKenna's specialty within the field of chemistry is organophosphorus chemistry. (Tr. at 545:7-10 (McKenna Dir.)). He has devoted his career to this specialized field of chemistry. (Tr. at 557:21-23 (McKenna Dir.)). Essentially all of Dr. McKenna's current work is in the field of organophosphorus chemistry. (Tr. at 546:4-5 (McKenna Dir.)).

46. Organophosphorus chemistry is the field of chemistry that is devoted to compounds that contain both carbon and phosphorus. (Tr. at 545:20-24 (McKenna Dir.)).

Bisphosphonates are a sub-class of organosphosphorus compounds. (Tr. at 546:6-14 (McKenna Dir.)).

47. Approximately 80% of Dr. McKenna's work is directed to bisphosphonates. (Tr. at 546:15-18 (McKenna Dir.)).

48. Dr. McKenna's work in the field of bisphosphonates began in the mid-1970s. (Tr. at 546:19-22 (McKenna Dir.)).

49. Dr. McKenna has published about 40 papers relating to bisphosphonates. (Tr. at 547:14-17 (McKenna Dir.)). His first paper directed to bisphosphonates was published in 1977. (Tr. at 546:23-547:1 (McKenna Dir.)).

50. Dr. McKenna has lectured or spoken at more than 100 scientific meetings or seminars, with approximately half of those being directed to bisphosphonates or related compounds. (Tr. at 548:15-23 (McKenna Dir.)).

51. Dr. McKenna is a named inventor on 15 patents or pending applications, the majority of which deal with bisphosphonates or related compounds. (Tr. at 549:2-9 (McKenna Dir.)).

52. Since 1995, Dr. McKenna has been on the International Scientific Board for the International Conference on Phosphorus Chemistry ("ICPC"). (Tr. at 549:10-24 (McKenna Dir.)). The ICPC meets bi-annually and is comprised of scientists from across the world devoted to phosphorus chemistry. (Tr. at 163:13-23; 164:18-165:3 (Lenz Cross)). The individuals on the ICPC's International Scientific Board are scientists who are working in the field of phosphorus chemistry and who are considered to be the leading scientists in that field. (Tr. at 550:1-551:15 (McKenna Dir.)).

53. Dr. McKenna is also on the editorial board of a journal called Molecular Pharmaceutics, published by the American Chemical Society, and he serves as a reviewer for approximately 20 other journals. (Tr. at 550:16-551:2 (McKenna Dir.)).

54. PTX 430 is a copy of Dr. McKenna's C.V., which contains an accurate summary of his educational background and professional experience through June 2005.

55. Dr. McKenna's testimony concerning the field of bisphosphonates for use in treating bone disease is based upon his having been an observer and a participant in the field for the last 20 years. (Tr. at 635:6-21 (McKenna Dir.)).

56. Dr. McKenna is an expert in organophosphorus chemistry, and in particular bisphosphonate chemistry.

4. Jocelyn McOsker

57. Jocelyn McOsker worked as a scientist for P&G from May 1985 until approximately 2001. (Tr. at 712:17-713:13 (McOsker Dir.)).

58. Ms. McOsker obtained a B.A. from Hope College in 1977 and a Master's degree in biochemistry from Cornell University in approximately 1985. (Tr. at 711:17-712:1 (McOsker Dir.)).

59. After graduating from Cornell, Ms. McOsker worked at Colgate University conducting studies on rats. (Tr. at 712:2-12 (McOsker Dir.)).

60. In May 1985, Ms. McOsker joined P&G as a research associate in the Bone Group. (Tr. at 712:13-713:7 (McOsker Dir.)). She worked for the Bone Group for several years developing animal models and screening new bisphosphonates in those models, including in the TPTX and Schenk assays (which are described in *infra* paragraphs 286 and 293, respectively). (Tr. at 713:8-16, 718:15-17, 719:19-21 (McOsker

Dir.)). Prior to joining P&G, she had experience running various types of animal models. (Tr. at 721:10-12 (McOsker Dir.)).

61. Eventually, Ms. McOsker was promoted to senior scientist in charge of the preclinical pharmacology program for risedronate. (Tr. at 713:17 (McOsker Dir.)).

62. In approximately 1995, Ms. McOsker transferred to P&G's Baby Care division, where she worked for another six years. (Tr. at 714:1-7 (McOsker Dir.)).

63. Subsequently, Ms. McOsker left P&G, went back to school and obtained her teaching certification, she is now a high school science teacher. (Tr. at 714:8-19 (McOsker Dir.)).

5. Dr. David Eastman

64. Dr. David Eastman worked as a scientist at P&G for approximately 24 years. (Tr. at 768:9-17, 769:10-13 (Eastman Dir.)).

65. Dr. Eastman received a Bachelor's degree in animal science and a Ph.D. in pharmacology and toxicology from University of California at Davis. Dr. Eastman obtained his Ph.D. in 1982. (Tr. at 768:2-8 (Eastman Dir.)).

66. Following completion of his Ph.D., Dr. Eastman went to work for P&G as a staff toxicologist. (Tr. at 768:9-14, 769:7-13 (Eastman Dir.)).

67. For much of his career at P&G, Dr. Eastman was a staff toxicologist or senior toxicologist involved in P&G's development of bisphosphonates. (Tr. at 769:7-23 (Eastman Dir.)).

68. Dr. Eastman designed the toxicity testing that P&G used in the mid-1980s to select bisphosphonates for potential use in treating osteoporosis and oversaw the execution and reporting of these studies. (Tr. at 769:24-770:11 (Eastman Dir.)).

69. Dr. Eastman retired from P&G in 2006, and now works as the Senior Director of Safety Sciences at Charles River Laboratories. (Tr. at 768:18-769:3 (Eastman Dir.)).

6. Dr. Scott Miller

70. Dr. Scott Miller is a Research Professor of Radiology, Civil and Environmental Engineering, and Adjunct Professor of Exercise and Sport Science, Nutrition at the University of Utah. He has been employed as a professor at the University of Utah since 1977. (Tr. at 830:17-831:10 (Miller Dir.); PTX 432).

71. Dr. Miller received a Bachelor of Science in biology from the University of Utah in 1970 and a Ph.D. in anatomy from the same institution in 1974. (Tr. at 831:13-16 (Miller Dir.)). Dr. Miller's dissertation focused on skeletal responses to two of the original bisphosphonates, ethane-1-hydroxy-1,1-diphosphonate (also known as "EHDP") and dichloromethylene diphosphonate (also known as "Cl_2MDP" or clodronate). (Tr. at 832:1-6 (Miller Dir.); PTX 432).

72. Dr. Miller specializes in radiobiology and bone disorders in particular. (Tr. at 832:9-12 (Miller Dir.)). He conducts preclinical studies in bone physiology, bone metabolism, bone endocrinology and pharmacology. (*Id.*) These studies are concerned with developing animal models, assays and test for understanding mechanisms of actions of drugs and mechanisms of bone physiology as they relate to human diseases. (Tr. at 832:13-20 (Miller Dir.)).

73. Dr. Miller has used TPTX assays throughout his career. (Tr. at 848:22-849:1 (Miller Dir.)).

74. Dr. Miller also has experience administering the Schenk assay. (Tr. at 845:11-13 (Miller Dir.)).

75. Dr. Miller has published over 200 articles relating to the treatment of human bone disease and more than a dozen articles specifically relating to bisphosphonates. (Tr. at 832:21-833:11 (Miller Dir.)).

76. Dr. Miller has served on the Editorial Board of the scientific journal *Bone* since 1989 and is currently an Associate Editor for the *Journal of Musculoskeletal and Neuronal Interactions*. Last year, he was a theme co-editor for a volume titled "Drug Delivery for Musculoskeletal Diseases" for the journal *Advanced Drug Delivery Reviews*. (Tr. at 835:11-836:2 (Miller Dir.); PTX 432).

77. Dr. Miller has served as a peer reviewer of scientific articles for numerous medical and scientific journals, many of which related to bisphosphonates or osteoporosis. (Tr. at 836:3-10 (Miller Dir.)).

78. Dr. Miller is also the named inventor on four issued or pending patents, two of which relate to bisphosphonates and osteoporosis and other bone diseases. (Tr. at 833:12-23 (Miller Dir.); PTX 432).

79. Dr. Miller is currently an investigator on a grant funded by the National Institutes of Health aimed at determining the ability of unique new therapeutic delivery platforms (specifically biopolymers) to deliver bisphosphonates and other bone targeting agents to skeletal tissues for the treatment of osteoporosis and other skeletal disorders. (Tr. at 833:24-834:13 (Miller Dir.); PTX 432).

80. Dr. Miller is also currently a principal investigator or co-investigator for three other funded grants from the National Institutes of Health. One grant is funded to study skeletal physiology and metabolism during pregnancy and lactation. Another grant is funded to define the biokinetics and metabolism of bone-seeking radionuclides, and the

other grant is funded to develop improved bone-targeting therapies for the treatment of osteoporosis. Dr. Miller also receives funding from the United States Department of Energy to study the health consequences of exposure to bone-seeking radioactive materials and also has several contracts with industry to develop novel bone therapeutic agents and skeletal targets. In addition, Dr. Miller recently received a grant from the United States government to research methods to remove radioactive metals from bone in the wake of dirty bomb incidents. (Tr. at 834:14-835:10 (Miller Dir.); PTX 432).

81. PTX 432 is a copy of Dr. Miller's C.V., which contains an accurate summary of his educational background and professional experience through March 2006.

82. Dr. Miller is an expert in the analysis of the effect of chemicals on bone structures with particular experience working with and analyzing bisphosphonate compounds and their effects on bone structure and development.

7. Dr. Daniel Smith

83. Dr. Daniel C. Smith is a Professor of Marketing, the Claire W. Barker Chair in Marketing, and Dean at the Kelley School of Business at Indiana University. (Tr. at 946:10-24 (Smith Dir.); PTX 434).

84. Dr. Smith joined Indiana University in 1996, and has served as Dean since 2004. (Tr. at 947:1-3, 17-20 (Smith Dir.); PTX 434). Previously, he taught at the University of Pittsburgh and the University of Wisconsin. (Tr. at 947:21-948:7 (Smith Dir.); PTX 434).

85. Dr. Smith has a Bachelor of Arts degree in business administration, a Masters of Business Administration with a focus in marketing, and a Ph.D. in marketing and strategy. (Tr. at 948:8-20 (Smith Dir.); PTX 434).

86. Dr. Smith's work in the field of marketing has focused on the interface between marketing strategy and customer decision making, an area in which he has published and for which he has been recognized by some of the leading journals in the field of marketing. (Tr. at 948:21, 949:21-950:18 (Smith Dir.)).

87. In particular, Dr. Smith has conducted research and taught in the area of pharmaceutical marketing, including an MBA program called "Healthcare Academy" at Indiana University, an executive education program with the Allegheny Health Education Research Foundation at the University of Pittsburgh, and as a consultant. (Tr. at 950:19-954:14 (Smith Dir.); PTX 434). Through these experiences, he has interviewed or spoken with numerous individuals, including physicians, and representatives of pharmaceutical companies, medical device companies, health care providers, and hospitals on topics relating to the role of marketing in physician prescribing behavior. (*Id.*)

88. PTX 434 is a copy of Dr. Smith's C.V., which contains an accurate summary of his educational background and professional experience.

B. Teva's Witnesses

1. Dr. George Lenz

89. Teva offered George R. Lenz, Ph.D. as an expert in the field of medicinal chemistry and pharmaceutical research. (Tr. at 66:15-17 (Lenz Dir.)).

90. Dr. Lenz was Teva's sole technical expert and Teva's only witness to provide testimony about the validity of the '122 patent. (Tr. at 148:15-149:5 (Lenz Dir.); Tr. at 334:1-3).

91. Dr. Lenz works for GRLEN R&D Associates. (Tr. at 49:3-4 (Lenz Dir.)). GRLEN R&D Associates provides consulting services to "small companies that are

interested in developing small molecule drugs." (Tr. at 49:21-24 (Lenz Dir.)). Dr. Lenz is the sole employee of GRLEN R&D. (Tr. at 169:2-4 (Lenz Cross)).

92. From 1969 to 1985, Dr. Lenz worked at G.D. Searle. (Tr. at 57:18-19 (Lenz Dir.)). According to Dr. Lenz, G.D. Searle "was an ethical pharmaceutical company" until it was acquired by Pfizer. (Tr. at 57:8-11 (Lenz Dir.)).

93. From 1985 to 1993, Dr. Lenz worked for the BOC Group, where he primarily worked on critical care drugs. (Tr. at 59:18-21, 60:6-10, 61:8-9 (Lenz Dir.)).

94. In 1993, Dr. Lenz started his own consulting business, George Lenz R&D. (Tr. at 61:12-13 (Lenz Dir.)).

95. Dr. Lenz has no formal education or training in bisphosphonates, osteoporosis, or the treatment of bone disease. (Tr. at 168:1-13 (Lenz Cross)).

96. DTX 134 is a copy of Dr. Lenz's C.V. submitted in connection with his expert report. (Tr. at 51:1 (Lenz Dir.); Tr. at 158:23 - 162:22 (Lenz Cross)).

97. At no time during his entire professional career as a chemist did Dr. Lenz ever work with bisphosphonates. (Tr. at 170:2-4 (Lenz Cross)). Dr. Lenz has never synthesized a bisphosphonate. (Tr. at 153:6-8 (Lenz Cross)). Dr. Lenz has never supervised any research concerning bisphosphonates, including risedronate. (Tr. at 157:14-19 (Lenz Cross)). Dr. Lenz had no experience with risedronate until he was hired by Teva to work on this case. (Tr. at 153:1-5; 182:11-13 (Lenz Cross)). In fact, before Teva hired Dr. Lenz as an expert in this case, he had absolutely no hands-on experience with any kind of bisphosphonate. (Tr. at 153:17-154:1 (Lenz Cross)).

98. In addition, Dr. Lenz has had no experience with the treatment of osteoporosis. (Tr. at 155:2-4 (Lenz Cross)). He has never treated patients with abnormal

calcium or phosphate metabolism, and has never worked with medical doctors who were treating bone diseases. (Tr. at 155:10-13 (Lenz Cross)). Dr. Lenz has never supervised any research directed to developing compounds for the treatment of osteoporosis, or any other metabolic bone disease. (Tr. at 157:20-158:1 (Lenz Cross)).

99. Of the 100 publications that Dr. Lenz claims to have written in the field of medicinal chemistry, none of them relate to either bisphosphonates or osteoporosis. (Tr. at 158:2-15 (Lenz Cross)). He has written only one article concerning a disease associated with abnormal calcium metabolism, however that article related to Steroids for the treatment of arthritis. (Tr. at 158:16-160:3 (Lenz Cross)).

100. Of the three books that Dr. Lenz has co-authored, none concern risedronate, bisphosphonates, organophosphorus compounds, the treatment of osteoporosis, or any other bone disease. (Tr. at 161:2-162:3 (Lenz Cross)).

101. Dr. Lenz has no patents concerning bisphosphonates, osteoporosis, or the treatment of diseases related to abnormal calcium or phosphate metabolism. (Tr. at 162:14-23 (Lenz Cross)).

102. Dr. Lenz has never attended any meetings of the International Conference on Phosphorus Chemistry or any other organization dedicated to the study of organophosphorus compounds, bisphosphonates, osteoporosis, or any other bone disease. (Tr. at 164:18-21, 165:4-6; 165:93-166:1 (Lenz Cross)). Dr. Lenz has not made or been asked to make any presentation on any of these subjects. (Tr. at 165:10-166:1 (Lenz Cross)).

103. Before Teva hired Dr. Lenz in this case, he had no specific knowledge of the nuances of the mechanism of action of bisphosphonates. (Tr. at 154:13-16 (Lenz Cross)).

104. Dr. Lenz has never conducted a Schenk assay and never requested that a Schenk assay be performed. (Tr. at 176:12-177:4 (Lenz Cross)). Before being hired by Teva for this case, Dr. Lenz had never reviewed or discussed the results of a Schenk assay. (Tr. at 176:23-177:7 (Lenz Cross)).

105. Similarly, during his entire career as a chemist, Dr. Lenz had never used or worked with the TPTX assay. (Tr. at 181:21-24 (Lenz Cross)).

106. Indeed, Dr. Lenz had never heard of either the Schenk assay or the TPTX assay before being hired by Teva as an expert witness in this case. (Tr. at 176:12-19, 180:15-20 (Lenz Cross)). Dr. Lenz admitted that if he had been one of the people working with bisphosphonates in the 1980s, he would have known about the Schenk assay before 2006. (Tr. at 178:2-6 (Lenz Cross)).

107. Having no education or experience with risedronate, bisphosphonates, or the treatment of osteoporosis, (Tr. at 182 (Lenz Cross)), Dr. Lenz went to the library to educate himself on these subjects after he was hired by Teva. (Tr. at 182:3-10 (Lenz Cross)). At the library, Dr. Lenz reviewed various patents and publications and conducted research on the Internet. (*Id.*).

108. To familiarize himself with bisphosphonates, Dr. Lenz reviewed the drug profiles of various bisphosphonates, including risedronate, etidronate and alendronate, in the current version of the Physician's Desk Reference. (Tr. at 182:21-183; 18, 193:18-194:10 (Lenz Cross)).

109. Dr. Lenz did not review the Physician's Desk Reference from 1984 because, according to him, he "was not able to do so" and "had no access to that" version. (Tr. at 194:11-15 (Lenz Cross)). Dr. Lenz was shown the 1984 Physician's Desk Reference during his testimony and acknowledged that the 1984 Physician's Desk Reference did not include drug profiles for risedronate, alendronate or clodronate. (Tr. at 194:16-195:16 (Lenz Cross); PTX 700).

2. Dr. Jesse David

110. Teva offered Dr. Jesse David as an expert in the field of economics. (Tr. at 293:7-9 (David Dir.)).

111. Since 1997, Dr. David has been employed by National Economic Research Associates ("NERA"). (Tr. at 289:23-290:1 (David Dir.)). NERA is a firm of economists that perform economic research for clients, primarily in the area of microeconomics. (Tr. at 290:4-8 (David Dir.)).

112. Dr. David submitted two expert reports in this case. (Tr. at 304:11-14 (David Cross)). His second expert report followed the Court's order granting Procter & Gamble's motion to strike Dr. David's first expert report because it was an inadmissible legal "opinion on the relevance of information related to commercial success." (Docket No. 66.) In total, Dr. David spent less than twenty hours preparing his expert reports. (Tr. at 310:13-16 (David Cross)).

113. In preparation for his expert reports and testimony in this case, Dr. David did not review any of the following information:

- deposition testimony taken in this case;
- prescription data for Actonel;
- Actonel's performance features or benefits;

- physician satisfaction with Actonel;
- sales volume of Actonel;
- profitability of Actonel;
- market share of Actonel;
- Actonel's revenue growth;
- R&D costs associated with Actonel;
- the market for Actonel and other osteoporosis drugs; and
- drugs competing with Actonel.

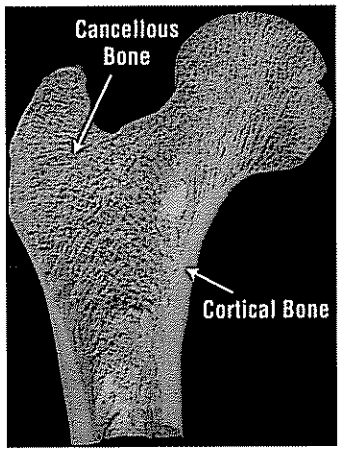
(Tr. at 310:17-314:95 (David Cross)). Dr. David testified that, in his view, none of this information was relevant to his opinion in this case. (Tr. at 314:6-9 (David Cross).

III. BACKGROUND OF OSTEOPOROSIS

A. The Structure of Bone and the Bone Remodeling Process

114. Bone has two major functions. One is as the scaffolding that keeps humans upright. The second is as a reservoir for calcium, phosphorus, magnesium, and other ions, which is a more dynamic function. (Tr. at 349:10-350:3 (Bilezikian Dir.)).

115. The picture below illustrates the two primary elements of bone.

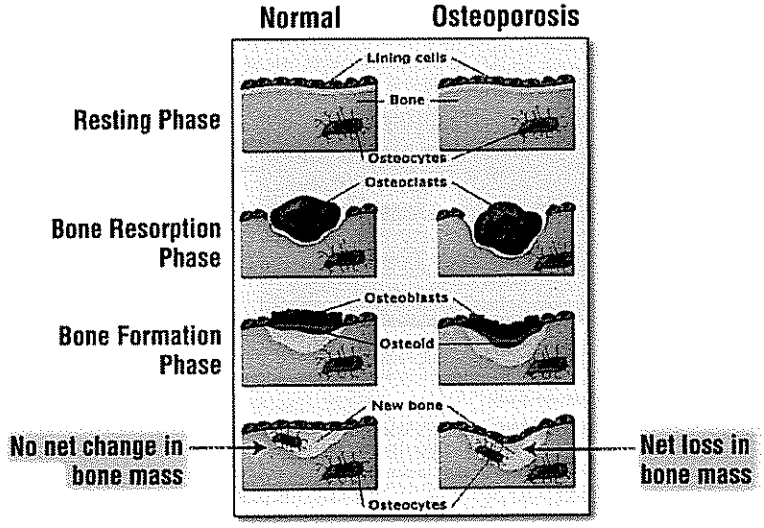


One arrow points to cortical bone and the second arrow points to cancellous bone. The cortical bone component is a thick, dense envelope of bone. Every bone has this thick, dense envelope. Cortical bone is metabolically sluggish and "turns over" only 1% or 2% per year. Cancellous bone is the finely articulated network of trabecular plates and struts that give bone the resiliency to withstand stress. Cancellous bone is metabolically very active, and "turns over" as much as 10% or 15% per year. (Tr. at 350:13-351:18 (Bilezikian Dir.); Slide P-10).

116. Bone is not a static material, and is in fact a dynamic organ. (Tr. at 351:24-352:6 (Bilezikian Dir.)).

117. Old, brittle, hypermature bone is routinely replaced with new, young resilient bone, through a process known as "bone remodeling." (Tr. at 353:5-9 (Bilezikian Dir.)).

118. The left hand side, slide P-11, of the picture below illustrates the normal process of bone remodeling.



(Tr. at 353:4-6 (Bilezikian Dir.); Slide P-11).

119. One cell that plays an important role in bone remodeling is called the "osteoclast." The osteoclast is a nucleated cell that has the job of breaking down and excavating a divot in the bone. That process can take anywhere from 2 to 4 or 5 weeks. (Tr. at 353:10-19 (Bilezikian Dir.)).

120. The part of the bone remodeling process during which the osteoclast breaks down the bone is known as "bone resorption." (Tr. at 356:24-357:5 (Bilezikian Dir.)).

121. The second cell that plays an important role in bone remodeling is called the "osteoblast." Osteoblasts are single nucleus cells and are not multi-nucleated. Osteoblasts come in and lay an organic matrix in the hole created by the osteoclast. The material that is laid down by the osteoblast is called an "osteoid" or Type I collagen. (Tr. at 353:20-354:6 (Bilezikian Dir.)).

122. Slide P-12 illustrates the footprint of an osteoclast, which has left a series of depressions ultimately to be filled in by the osteoblast. (Tr. at 357:13-358:4 (Bilezikian Dir.)).

123. Once the collagen matrix has been laid down by the osteoblast, calcium mineral is deposited into the collagen matrix to harden the new bone material. This process is called "mineralization." (Tr. at 358:8-13 (Bilezikian Dir.)).

124. The part of the bone remodeling process during which the collagen matrix is laid down and then mineralized is known as "bone formation." (Tr. at 353:20-354:16 (Bilezikian Dir.)).

125. The bone remodeling process may take anywhere from three to five months. (Tr. at 353:5-9 (Bilezikian Dir.)).

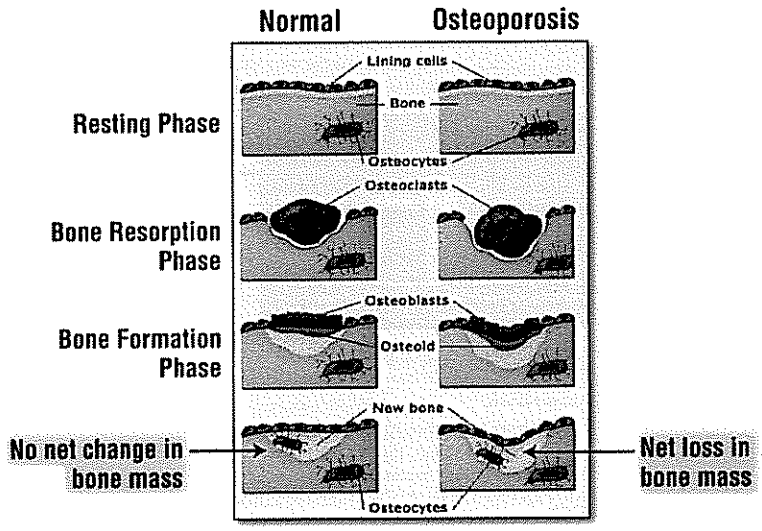
126. In a normal individual, as much bone is replaced as is lost during the bone remodeling process. (Tr. at 354:17-22 (Bilezikian Dir.)).

B. Osteoporosis and its Causes

127. "Metabolic bone diseases" are disorders of the skeleton. (Tr. at 338:6-8 (Bilezikian Dir.)).

128. Osteoporosis is recognized as the most important metabolic bone disease. (Tr. 338:8-9 (Bilezikian Dir.)).

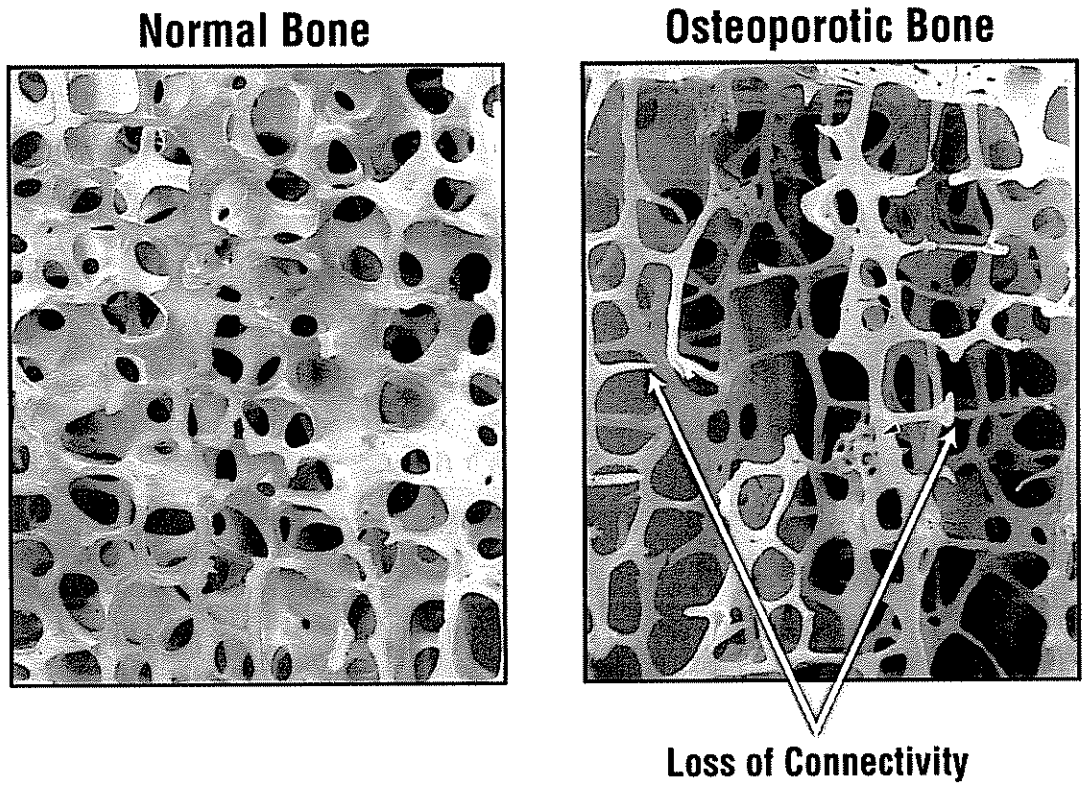
129. Scientists today believe that the crux of osteoporosis is an abnormality in the bone remodeling process. The right hand side of slide the picture below illustrates this abnormal situation.



Instead of the osteoclast taking a reasonably-sized piece of bone ultimately to be replaced, it takes a bigger bite out of the bone. Additionally, the osteoblast is unable to replace the entire amount of material taken by the osteoclast and, at the end of the sequence, one has less bone than at the beginning. (Tr. at 355:1-16 (Bilezikian Dir.); Slide P-11).

130. Osteoporosis is defined as a disorder of bone strength, which in turn is defined by bone density. (Tr. at 358:15-19 (Bilezikian Dir.)).

131. The picture below illustrates the contrast between the normal and osteoporotic bone.



In normal bone, the microarchitecture of bone illustrates good connectivity, and good separation between the trabecular struts of the normal bone tissue. By contrast, osteoporotic bone has less bone and the trabecular struts (which are indicated by the arrows) are separated from each other, and there are fewer of them. This disorder of compromised bone strength leads to fractures. (Tr. at 358:23-359:16 (Bilezikian Dir.); Slide P-13).

132. There are multiple factors that cause osteoporosis. The most common cause of osteoporosis is the lack of estrogen in post-menopausal women. It appears that

the lack of estrogen leads to a phase of accelerated bone resorption. (Tr. at 359:18-360:11 (Bilezikian Dir.)).

133. In the United States, over 12 million individuals are afflicted with osteoporosis. If one adds to that number the additional individuals who are at significant risk of developing osteoporosis, upwards of 40 to 45 million individuals in the United States are affected by osteoporosis. (Tr. at 360:12-361:6 (Bilezikian Dir.)).

134. Individuals who are more likely to develop osteoporosis include postmenopausal women and those who have had disorders treated by glucocorticoids. (Tr. at 361:7-361:24(Bilezikian Dir.)).

135. Approximately 25% of the osteoporotic population is male. (Tr. at 362:4-9 (Bilezikian Dir.)).

136. Osteoporosis takes a great physical toll on patients and has a high human cost, as depicted in slides P-14a and P-14b. (Tr. at 363:20-365:3 (Bilezikian Dir.); P-14a; and P-14b).

137. In the United States, approximately 1.5 million osteoporosis fractures occur each year, including approximately 300,000 hip fractures, which is the most serious fracture resulting from osteoporosis. (Tr. at 362:10-21 (Bilezikian Dir.)).

138. Many individuals who sustain hip fractures due to osteoporosis need help just to walk and become dependent on long-term health care. Twenty-five percent of individuals as a group who have sustained a hip fracture are likely to die within one year of the fracture. (Tr. at 362:22-263:13 (Bilezikian Dir.)).

139. Osteoporosis also has a very large economic impact. Between $17 and $20 billion dollars a year is spent each year on the care of patients with osteoporosis. (Tr. at 363:14-363:19 (Bilezikian Dir.)).

C. The Need for Safe and Effective Treatments for Osteoporosis in the Mid-1980s

140. The status of knowledge about osteoporosis in the art in the 1980s was "embryonic." (Tr. at 365:14-17 (Bilezikian Dir.)).

141. In the 1980s, only two treatments were available for osteoporosis: estrogen therapy and calcitonin treatment. (Tr. at 366:14-368:22 (Bilezikian Dir.)).

142. Estrogen therapy presented some serious difficulties, including cerebral vascular events, an increase in strokes, a condition called thrombophlebitis, cardiovascular abnormalities, and an increase in breast cancer. (Tr. at 367:11-20 (Bilezikian Dir.)).

143. Calcitonin was a natural hormonal product, but it had to be administered with a needle on a daily basis and was very expensive. For these and other reasons, calcitonin never became a wide-spread treatment for osteoporosis. (Tr. at 368:9-22 (Bilezikian Dir.)).

144. In the mid-1980s, scientists also considered using fluoride as a treatment for osteoporosis. (Tr. at 368:23-369:6 (Bilezikian Dir.)).

145. Fluoride has the property of stimulating the osteoblast cells, which in turn leads to a dramatic increase in bone density, anywhere from 8% to 9% per year over a five-year period. Because increases in bone density were at the time the FDA's benchmark for therapeutic efficacy, fluoride was initially considered to be a very effective treatment for osteoporosis. (Tr. at 369:16-370:5 (Bilezikian Dir.)).

146. Fluoride was in fact found, however, to be an ineffective treatment for osteoporosis because judged by the true end-point, namely the reduction in incidents of fracture, fluoride was no different than placebo. In fact, in some studies, fluoride caused an increase in fractures. (Tr. at 370:7-12 (Bilezikian Dir.)).

147. The experience with fluoride caused the FDA to recognize that one could not depend on changes in bone density to measure efficacy in treatment of osteoporosis; instead, one needed to measure the reduction in bone fractures. (Tr. at 370:16-371:9 (Bilezikian Dir.)).

148. In the early and mid-1980s, there existed a need for a drug that was a safe and efficacious treatment for osteoporosis. (Tr. at 371:10-21 (Bilezikian Dir.)).

IV. BACKGROUND OF BISPHOSPHONATES

A. Structure of Bisphosphonates

149. A bisphosphonate is a chemical compound having two phosphonate (PO_3) groups, joined to one or more carbon (C) atoms. (Tr. at 546:10-14 (McKenna Dir.)).

150. A phosphonate group includes a single "P," which is phosphorus, three "O" atoms, which are oxygen, and two "H" or hydrogen atoms, wherein the "P" is attached to the geminal carbon atom. One "O" atom is attached to the "P" by a double (2) bond, while the other two "O"s are attached to the "P" by a single (1) bond. Each "H" is attached to one of the single-bonded "O"s. (Tr. at 560:5-7 (McKenna Dir.); P-20 (in orange)).

151. In a "geminal bisphosphonate," the phosphonate groups are attached to the same carbon atom, which is referred to as the "geminal carbon" atom. (Tr. at 561:11-12, 17-20 (McKenna Dir.)).

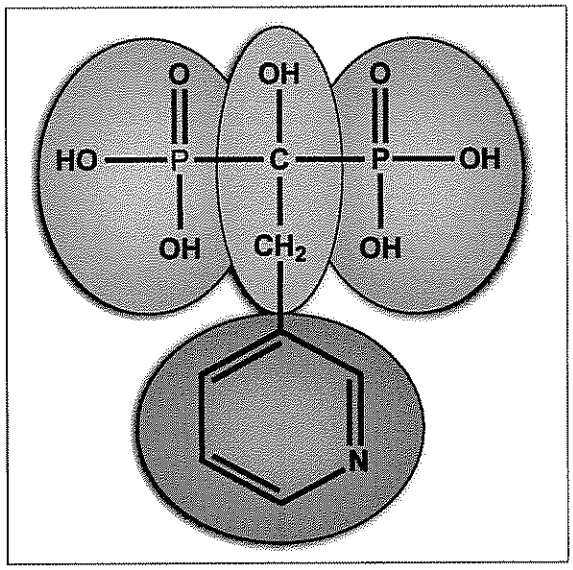
152. Bisphosphonates are sometimes referred to as diphosphonates. (Tr. at 68:17-69:4 (Lenz Dir.)).

153. A "bisphosphonate" is the salt form of a "bisphosphonic acid." (*See, e.g.*, PTX 22 at PG 23092; PTX 88 at PG 57087).

1. The Structure of Risedronate

154. Risedronate is the common name given to the compound 2-(3-pyridyl)-1-hydroxyethane-1,1-diphosphonic acid. (Tr. at 559:21-560:1 (McKenna Dir.)).

155. The structure of risedronate is:



(Tr. at 559:21-560:1 (McKenna Dir.); Slide P-20).

156. The "1,1-diphosphonic acid" refers to the two phosphonic acid groups shown in upper left and upper right of the diagram above that are both attached to the first or "1" carbon atom. (Tr. at 560:5-7 (McKenna Dir.); Slide P-20).

157. The "1-hydroxyethane" refers to the portion of the structure shown in upper middle above, *i.e.*, a 2-carbon chain that is the backbone of the compound. (Tr. at 560:7-8, 561:10-16. (McKenna Dir.); Slide P-20). "1-hydroxyethane" indicates that the

compound has a hydroxyl group attached to the first carbon atom in the chain. (Tr. at 561:10-12 (McKenna Dir.)).

158. A pyridyl group is the 6-membered aromatic ring structure shown in lower part of the diagram above that contains a single nitrogen atom. (Tr. at 560:8-15 (McKenna Dir.)).

159. In the name "2-(3-pyridyl)," the "2" refers to the fact that the pyridyl group is attached to the second carbon in the carbon chain. (Tr. at 561:7-16; 561:21-562:3 (McKenna Dir.)). The "3" refers to the fact that the pyridyl ring is attached to the carbon chain at the "3-position" of the pyridyl ring. (Tr. at 562:13-16 (McKenna Dir.)). The nitrogen is designated as position "1" on the ring, and the ring is attached to the carbon chain two positions away from the nitrogen; thus it is attached at the "three position" of the pyridyl ring. (Tr. at 562:7-16 (McKenna Dir.)).

B. Understanding of Bisphosphonates for Use in Treating Osteoporosis in the Mid-1980s

1. Use of Bisphosphonates in the Mid-1980s to Treat Bone Disorders

160. Bisphosphonates have been known since at least the 1880s, but had only been used for industrial applications, such as stopping calcium deposits in pipes. (Tr. at 372:8-24 (Bilezikian Dir.)).

161. As of 1984, no bisphosphonate was approved in the United States for the treatment of osteoporosis. (Tr. at 196:9-15 (Lenz Cross)).

162. In the early 1980s, researchers were studying bisphosphonates as potential treatments for osteoporosis. (Tr. at 243:4-10 (Lenz Cross); Tr. at 371:22-372:5 (Bilezikian Dir.)). In particular, scientists were looking to find more potent and safer treatments. (Tr. at 243:22-244:2 (Lenz Cross)).

163. The first bisphosphonates studied as potential drugs were EHDP (also known as "etidronate" or "Didronel") and clodronate. (Tr. at 373:4-11 (Bilezikian Dir.)).

164. Although etidronate was approved by the Food and Drug Administration for treatment of Paget's disease, which is another metabolic bone disease, it was never approved for treatment of osteoporosis. Although the precise reasons for the failure of the FDA to approve etidronate for osteoporosis is not known, it is likely linked to the fact that there was no evidence at the time that etidronate reduced bone fractures, only that it increased bone density. In addition, the failure to approve etidronate may have been due to concerns that, because it is a relatively impotent bisphosphonate, it could potentially be associated with the impairment of bone mineralization. (Tr. at 338:21-23, 373:12-375:5 (Bilezikian Dir.); Tr. at 196:1-8 (Lenz Cross)).

165. For a bisphosphonate to be used in treating osteoporosis, the therapeutic index is the differential between the dose that must be given to a patient to inhibit bone resorption and the dose that begins to cause toxicity problems, such as inhibition of bone mineralization or some other toxic effect. The wider the therapeutic index, the easier it is to treat patients and to get the beneficial effects of the drug without getting undesirable side effects. (Tr. at 423:17-424:18 (Benedict Dir.)).

166. Slide P-15 illustrates the problem with etidronate. A clinically effective dose of etidronate would be 400 milligrams, but at 800 milligrams there was clear evidence that etidronate would inhibit the process of bone mineralization. Therefore, the therapeutic index of etidronate is only 2:1, and long-term, chronic treatment with etidronate thereby runs the risk of substituting the disease of osteoporosis for another

disease, namely that of impaired bone mineralization. (Tr. at 375:6-24 (Bilezikian Dir.); Tr. at 609:4-9 (McKenna Dir.); Tr. at 246:8-11 (Lenz Cross); P-15).

167. Impaired bone mineralization means that the individual has lost the last phase of bone remodeling. Therefore, the patient would have a skeleton impaired by osteomalacia, which is the Greek term for "soft bone." (Tr. at 376:1-11 (Bilezikian Dir.)).

168. Slide P-16 shows an example of osteomalacia. The arrows point to a linear lucency, which is essentially a hole in the bone. These are also known as "pseudo fractures." They are not true fractures; they are simply parts of the bone that have not properly remodeled. (Tr. at 376:12-24 (Bilezikian Dir.); P-16).

169. Etidronate is approved in the United States for the treatment of Paget's disease, but the impairment of bone mineralization is not as much of a concern when treating Paget's disease as it is for the chronic treatment of osteoporosis. (Tr. at 377:1-22 (Bilezikian Dir.)).

170. Clodronate was also considered a potentially promising bisphosphonate treatment for osteoporosis in the early 1980s, but six cases of acute leukemia occurred in patents taking clodronate and further development of the drug was stopped. (Tr. at 377:23-378:15 (Bilezikian Dir.)). As a result, clodronate was never marketed in the United States. (Tr. at 245:4-7 (Lenz Cross)).

171. The various concerns about etidronate and clodronate in the early 1980s stimulated a search for other bisphosphonate, that would be more potent than etidronate or clodronate and therefore would have a wider therapeutic index. (Tr. at 378:17-379:7 (Bilezikian Dir.); Tr. at 248:8-11 (Lenz Cross)).

172. Dr. Lenz admitted that clodronate and etidronate did not solve the problem of the need for a more potent, less toxic drug to treat osteoporosis. (Tr. at 246:12-15 (Lenz Cross)). Instead, etidronate and clodronate led scientists looking for more potent, less toxic drugs for the treatment of osteoporosis in a variety of different directions. (Tr. at 248:8-11 (Lenz Cross)). As a result, scientists in the mid-1980s were studying a large number of different bisphosphonates. (Tr. at 248:12-249:8 (Lenz Cross)). P&G alone studied hundreds of bisphosphonates. (Tr. at 248:17-20 (Lenz Cross)).

173. The bisphosphonate pamidronate has never been approved in the United States for treatment of osteoporosis. (Tr. 379:8-380:1 (Bilezikian Dir.)).

174. The bisphosphonate alendronate, which is sold under the brand name Fosamax, was not approved for treatment of osteoporosis in the United States until 1995. (Tr. 379:14-20 (Bilezikian Dir.)).

175. Ibandronate is the newest of the bisphosphonates. It became available for treatment of osteoporosis in the United States only in the past year and a half. (Tr. at 384:8-12 (Bilezikian Dir.)).

176. The bisphosphonate 2-pyr EHDP has never been approved for the treatment of osteoporosis and has never been commercially marketed as a treatment for any disease. (Tr. at 150:8-18 (Lenz Cross)).

2. Understanding of Mechanisms of Action of Bisphosphonates in the Mid-1980s

177. Dr. Lenz's assertion that there was an understanding of the mechanisms of action of bisphosphonates in the mid-1980s is wrong. (Tr. at 579:22-580:2 (McKenna Dir.)).

178. In the mid-1980s, very little information was available regarding how bisphosphonates worked in the treatment of bone disease. (Tr. at 837:12-21 (Miller Dir.)).

179. In the mid-1980s, there was speculation about how bisphosphonates worked. For example, some believed that the nitrogen-containing bisphosphonates worked by neutralizing acid in the osteoclasts. (Tr. at 580:16-21 (McKenna Dir.)). This, however, turned out to be incorrect. (Tr. at 580:22-24 (McKenna Dir.)).

180. An understanding of how bisphosphonates work in treating osteoporosis is only now emerging through the use of techniques and technologies that did not exist and information that researchers did not have access to in the mid-1980s. (Tr. at 579:22-580:15 (McKenna Dir.)). Such techniques, technology, and information include x-ray crystallographic determinations of sites of action, demonstrations that those enzymes are in fact sites of action, and knowledge of the molecular structure of those sites and how they interact with the drug. (Tr. at 579:22-580:15 (McKenna Dir.)).

3. Understanding of the Structure-Activity Relationships of Bisphosphonates in the Mid-1980s

181. The phrase "structure-activity relationship" means a formal study of a fairly significant body of compounds that are varied with respect to some activity, typically a biological activity. An attempt is then made to correlate the data such that the activity can be explained by the structure in every case. (Tr. at 565:1-10 (McKenna Dir.)).

182. While there were various bisphosphonates known in the mid-1980s, some for treatment of bone diseases, such as Paget's disease, there was no reliable

understanding of the structure-activity relationships of these bisphosphonates. (Tr. at 565:11-15 (McKenna Dir.); Tr. at 837:22-838:6 (Miller Dir.)).

183. In the mid-1980s, there was no clear and reliable understanding of the factors that would determine the relative activities of bisphosphonates. (Tr. at 565: 24-566:5 (McKenna Dir.)).

184. In the mid-1980s, there was no clear and reliable understanding of which bisphosphonates would be toxic and which would not. (Tr. at 566:6-9 (McKenna Dir.)).

185. In the mid-1980s, the only way to determine if a bisphosphonate was effective was to put it through experimental testing. (Tr. at 840:8-15 (Miller Dir.)).

186. In the mid-1980s, and even today, the only way to determine if a bisphosphonate was safe was to put it through experimental testing. (Tr. at 840:16-21 (Miller Dir.)).

187. In the mid-1980s, there was no clear understanding of the effect that modifying the structure of a bisphosphonate would have on its biological activity. (Tr. at 566:24-567:5 (McKenna Dir.)).

188. Researchers in the field in the mid-1980s had observed that small changes in structure could have no effect, a small effect or a large effect on a bisphosphonates properties. (Tr. at 567:5-9 (McKenna Dir.)).

189. For example, in U.S. Patent No. 4,621,077 (the "'077 patent"), the patent covering alendronate, one of the prior art bisphosphonates on which Teva relies, the inventors stated:

> [O]ne must also consider that the surprisingly high activity [of the claimed bisphosphonate] could not have been foreseen on the basis of the chemical structure insofar as it has been ably demonstrated that even small structural

> variations can result in substantial differences from the point of view of activity as well as tolerability of the substances.

(DTX 42 at col. 14:7.) The '077 patent was filed in 1984 and issued in 1986. (Tr. at 228:10-15 (Lenz Cross); DTX 42). Dr. Lenz admitted that the inventors of the '077 patent were in a better position than he was to express the state of the art of in 1984. (Tr. at 229:6-12 (Lenz Cross)).

190. It was generally recognized by people working in the field in the mid-1980s that the activity of bisphosphonates was unpredictable. (Tr. at 567:14-18 (McKenna Dir.); Tr. at 838:7-12 (Miller Dir.)).

191. For example, in the 1980s Dr. Herbert Fleisch authored or co-authored numerous publications in which he discussed the unpredictable nature of bisphosphonates. *See* (Tr. at 567:19-579:5 (McKenna Dir.); PTX 356; PTX 355; PTX 460; PTX 461). Dr. Fleisch is regarded as a pioneer and a founder of the study of bisphosphonates as potential drugs for the treatment of bone disease. (Tr. at 568:3-8 (McKenna Dir.); Tr. at 382:15-383:9 (Bilezikian Dir.)). In the opinion of Dr. Bilezikian, people in the field rely on Dr. Fleisch's opinions routinely. (Tr. at 383:10-18 (Bilezikian Dir.)).

192. Teva's expert, Dr. Lenz, acknowledged that, even though he had not heard of Dr. Fleisch before being retained in this case, Dr. Fleisch was one of the leading authorities on bisphosphonates in the 1980s, and "a very important man in the field of bone chemistry." (Tr. at 230:7-12, 234:3-4 (Lenz Cross)).

193. PTX 356 is a 1983 article co-authored by Dr. Fleisch, which was published in *Calcified Tissue International* and entitled "Structure-Activity Relationships of Various Bisphosphonates."

194. In PTX 356, the authors reviewed the available data on activities of bisphosphonates to determine if a discernible pattern existed. (Tr. at 569:17-21 (McKenna Dir.)).

195. Dr. Fleisch and his colleagues concluded that:

> Finally, these results show that the various bisphosphonates vary a great deal in their respective effects. This implies that ***every one of them has to be considered as a compound per se***, their structure of bisphosphonates only making them go specifically to bone and other mineralized tissues.

(PTX 356 at 98 (emphasis added); Tr. at 568:17-570:10 (McKenna Dir.)).

196. According to Dr. McKenna, this statement accurately characterizes the state of the field in the mid-1980s and confirms the view at that time, "individual compounds have to be considered individually." (Tr. at 570:21-571:3 (McKenna Dir.)).

197. PTX 355 is paper by Dr. Fleisch entitled "Chemistry and Mechanisms of Action of Bisphosphonates," published in *Monographs of The Mario Negri Institute for Pharmacological Research*, Milan, Italy, and is based on a symposium held in 1984. (PTX 355; Tr. at 571:14-24) (McKenna Dir.)).

198. In PTX 355, Dr. Fleisch stated:

> It has to be emphasized that every compound, while remaining a bisphosphonate, exhibits its own physical-chemical, biological and therapeutic characteristics, so that each bisphosphonate has to be considered on its own. ***To infer from one compound the effects in another is dangerous and can be misleading***.

PTX 355 at 33 (emphasis added); Tr. at 572:9-573:1 (McKenna Dir.)).

199. With respect to structure-activity relationships, Dr. Fleisch observed:

> The potency of inhibiting bone resorption varies widely between different bisphosphonates and ***no relation has yet***

> ***emerged between the structure of the bisphosphonate and its effect on bone resorption***.

(PTX 355 at 37 (emphasis added); Tr. at 573:12-16 (McKenna Dir.)).

200. In PTX 355, Dr. Fleisch concluded:

> Based on their action on calcium phosphate crystal formation and on bone resorption, the geminal bisphosphonates represent a new class of drugs with considerable therapeutic potential. ***The fact that their mode of action, especially with respect to bone resorption, remains unknown, reflects our poor knowledge about the physiological mechanisms involved in this process***.

(PTX 355 at 38 (emphasis added); Tr. at 574:7-15 (McKenna Dir.)).

201. According to Dr. McKenna, these statements in PTX 355 accurately reflect the state of the field in the mid-1980s. (Tr. at 573:4-6; 574:1-3, 575:5-7 (McKenna Dir.)).

202. PTX 460 is an article by Dr. Fleisch entitled "Bisphosphonates, Pharmacology and Use in the Treatment of Tumor Induced Hypercalcemic and Metastatic Bone Disease," published in a journal called *Drugs* in 1991. (PTX 460; Tr. 575:8-19) (McKenna Dir.)).

203. In PTX 460, Dr. Fleisch stated:

> It has emerged that ***small changes in the structure of the bisphosphonates can lead to extensive alterations in their physicochemical, biological, therapeutic and toxicological characteristics. . . . It means however that we cannot necessarily extrapolate results from one compound to others***, and that it is not correct to talk generally of the "effects of bisphosphonates." Each bisphosphonate has to be considered.

(PTX 460 at 921 (emphasis added); Tr. at 576:1-12 (McKenna Dir.)).

204. Dr. Fleisch also stated that "[t]he mechanism of bisphosphonate inhibition of bone resorption is still not clear." (PTX 460 at 924; Tr. at 577:11-24 (McKenna Dir.)).

205. These statements by Dr. Fleisch were accurate characterizations of the state of understanding of bisphosphonates as of 1991. (Tr. at 576:15-17, 577:23-24 (McKenna Dir.)).

206. PTX 461 is a monograph by Dr. Fleisch entitled "Bisphosphonates in bone disease: From the laboratory to the patient," published in 1993, in which Dr. Fleisch discussed many aspects of bisphosphonates for the treatment of bone disease. (PTX 461; Tr. at 578:1-15 (McKenna Dir.)).

207. In PTX 461, Dr. Fleisch stated:

> Each bisphosphonate has its own physicochemical and biological characteristics. ***This variability in effect makes it impossible to extrapolate with certainty from data for one compound to others, so that each compound has to be considered on its own, both with respect to its use and its toxicology***.

(PTX 461 at 29 (emphasis added); Tr. at 578:16-23 (McKenna Dir.)).

208. This statement by Dr. Fleisch correctly states the understanding of those in the field of bisphosphonates in 1993. (Tr. at 579:2-5 (McKenna Dir.)).

209. In the 1980s, based upon a bisphosphonate's structure, it was not possible to predict whether a particular bisphosphonate would be useful as a drug for treating osteoporosis. (Tr. at 563:17-23 (McKenna Dir.)). It was not possible to predict the efficacy of a bisphosphonate based upon its structure. (Tr. at 563:24-564:3 (McKenna Dir.)). Nor was it possible to predict the toxicity of a bisphosphonate based upon its structure. (Tr. at 564:4-5 (McKenna Dir.)).

210. Such predictions were not possible in the mid-1980s because of the poor understanding researchers had of the mechanisms of action and the structure-activity relationships of bisphosphonates:

> In order to make such a prediction, I would have to have various kinds of knowledge which were not available at that time. For example, simply to predict the potency of the drug with respect to its binding to a particular target, perhaps an enzyme or a receptor, I would have to know what is that receptor or what is that enzyme. To really understand the nature of this process in addition, I would have to know the intimate molecular structure of that active site as we referred to, as the deactive site of the receptor or the enzyme to understand how that interaction might take place.

(Tr. at 564:8-21 (McKenna Dir.)).

C. Definition of Person of Ordinary Skill in the Art in the Mid-1980s

211. In the mid-1980s, the art relevant to the '122 patent relates to "pharmaceutical compositions containing geminal [bis]phosphonates," (JTX 1, Col. 1:1-2,) "which are useful in treating or preventing diseases characterized by abnormal calcium and phosphate metabolism, in particular those which are characterized by abnormal bone metabolism." (JTX 1, Col. 1:13-15).

212. In 1985, a person of ordinary skill in the art relevant to the '122 patent would have had at least a Ph.D. in synthetic or bio-organic chemistry, as well as additional training in phosphorus chemistry, involving either a post-doctoral program or industry experience researching or working with such compounds. (Tr. at 555:18-24, 558:6-11 (McKenna Dir.)).

213. Training and experience with organophosphorus compounds would be required because of the special nature of organophosphorus and bisphosphonate compounds. (Tr. at 556:1-3, 558:21-559:4 (McKenna Dir.)).

214. Organophosphorus compounds, including bisphosphonates are unique because they contain the element phosphorus, which distinguishes them from other types of organic compounds. (Tr. at 556:1-6 (McKenna Dir.)). This is particularly true in the

area of pharmaceuticals because of the significant role that phosphorus plays in many biomolecules, such as DNA, ADP (the molecule responsible for energy transactions with many enzymes), and bone. (Tr. at 556:9-17 (McKenna Dir.)).

215. The unique nature of organophosphorus compounds has been recognized in the field of chemistry in various ways. For example, there is a journal dealing with phosphorus chemistry known as *Phosphorus, Sulfur, Silicon and Related Elements*, formerly *Phosphorus, Sulfur*. Further, in the monograph series *Science of Synthesis*, which is a compilation of information about the synthesis of an enormous range of chemical compounds, there are special sections devoted to phosphorus-containing compounds. In addition, esteemed scientists, such as Dr. McKenna, have devoted their careers to the study of phosphorus chemistry. (Tr. at 556:18-557:23 (McKenna Dir.)).

216. Teva's expert, Dr. Lenz, testified that a person of ordinary skill in the art in the 1980s would have knowledge of the pharmacology and mechanism of action of bisphosphonates. (Tr. at 202:20-24 (Lenz Cross)).

217. Before Teva hired Dr. Lenz in this case, he had no specific knowledge of the nuances of the mechanism of action of bisphosphonates. (Tr. at 154:13-16 (Lenz Cross)).

218. All of the opinions offered by Dr. Lenz during his testimony were dependent upon his definition of one of ordinary skill in the art. (Tr. at 199 (Lenz Cross)). Dr. Lenz admitted that he offered no opinions on whether the invention of the '122 patent would have been obvious to a person of ordinary skill in the art as defined by Dr. McKenna. (Tr. at 200:9-14 (Lenz Cross)).

219. Dr. McKenna was a person of ordinary skill in the art in the mid-1980s. (Tr. at 559:5-8 (McKenna Dir.); *see also* PTX 430).

220. Teva's expert, Dr. Lenz, admitted that "[b]ack in the middle of the 1980s [he] did not work in bisphosphonates or phosphorus chemistry." (Tr. at 203:7-9 (Lenz Cross)).

V. THE DISCOVERY OF RISEDRONATE

A. Dr. Benedict's Conception and Synthesis of Risedronate

221. Dr. Benedict first conceived of risedronate in May 1984. (Tr. at 453:1-12 (Benedict Dir.); PTX 69 at PG 53860).

222. He made risedronate for the first time in May 1985. (Tr. at 420:22-421:1 (Benedict Dir.)). Dr. Benedict was the first person to make risedronate. (Tr. at 420:19-21 (Benedict Dir.)).

223. Dr. Lenz did not dispute that Dr. Benedict was the first person to conceive of and make risedronate. (Tr. at 250:3-15 (Lenz Cross)).

224. Dr. Lenz did not dispute the date on which Dr. Benedict first conceived risedronate or the date on which Dr. Benedict first made risedronate. (Tr. at 250:3-15 (Lenz Cross)).

225. At the time Dr. Benedict first made risedronate, he was part of a research group at P&G looking for the "next generation" of bisphosphonates to treat bone diseases, such as osteoporosis, Paget's Disease and metastatic cancers. (Tr. at 415:7-12, 421:5-11, 423:13-16 (Benedict Dir.)).

226. When Dr. Benedict joined P&G in 1974, P&G was investigating various bisphosphonates for use in treating metabolic bone diseases, including Didronel (etidronate) and clodronate. (Tr. at 416:12-20 (Benedict Dir.)). P&G was aware that

both of these compounds had problems. In the case of Didronel, there were concerns that at the doses needed to effectively inhibit bone resorption, the drug also inhibited bone mineralization, so bones became "soft." Clodronate was suspected of being associated with cancer. (Tr. at 416:6–22, 421:17–422:1, 422:13-423:12 (Benedict Dir.)).

227. Dr. Benedict's goal at P&G was to find compounds that would be very potent in inhibiting bone resorption, and to increase the magnitude of the difference between the dose at which the compounds would inhibit bone resorption (*i.e.*, the lowest dose possible) and the dose at which the compounds would impact bone mineralization (*i.e.*, the highest dose possible). (Tr. at 423:17-424:3 (Benedict Dir.)). In other words, Dr. Benedict was "trying to widen the therapeutic index." (Tr. at 424:2-3) (Benedict Dir.)).

228. Although P&G wanted to be able to predict the efficacy of a bisphosphonate based on its structure, it found that, in order to know whether a particular compound was effective (or which compound would be most biologically effective), especially with respect to inhibition of bone resorption, it actually had to make and test each compound. (Tr. at 425:8-426:8 (Benedict Dir.); Tr. at 530:11-20 (Benedict Cross)). Likewise, P&G found that it was even more difficult to predict the toxicity of a bisphosphonate. (Tr. at 428:17-429:2 (Benedict Dir.); Tr. at 530:11-20 (Benedict Cross)). Accordingly, without making and testing a particular bisphosphonate, it was not possible for P&G to predict the therapeutic index of any compound. (Tr. at 426:5-8, 428:17-429:2 (Benedict Dir.)).

229. Therefore, in its endeavor to find the "next generation" bisphosphonate, P&G made "hundreds" of different bisphosphonate compounds. (Tr. at 427:10-21 (Benedict Dir.)).

230. In order to determine the therapeutic index for a particular bisphosphonate, P&G ran various tests, including the crystal-growth inhibition test, which was a laboratory model for inhibition of bone mineralization, a "TPTX" assay, which was an animal model for inhibition of bone resorption, and a "Schenk" test, which was another animal model to evaluate the ability of compounds to inhibit bone resorption. (Tr. at 426:13-427:9 (Benedict Dir.)). In addition, to determine the level of toxicity of a particular bisphosphonate, P&G ran toxicity tests. (Tr. at 428:17-24 (Benedict Dir.)).

231. The reason P&G made "hundreds" of bisphosphonates was because they "kept getting surprised," especially by the results of the tests to determine the ability of a compound to inhibit bone resorption. (Tr. at 428:5-16 (Benedict Dir.)).

232. In connection with his work, Dr. Benedict typically would prepare a research proposal describing the research that he planned to undertake. (Tr. at 429:3-11 (Benedict Dir.)).

233. PTX 117 is a research proposal dated June 2, 1983 that Dr. Benedict and Dr. Christopher Perkins prepared suggesting that, in order to avoid some of the issues associated with etidronate-namely its inhibition of bone mineralization, they wanted to make some cyclic bisphosphonates that bound less tightly to bone. The logic behind this proposal was that if the compounds bound less tightly to bone, they would be less potent inhibitors of bone mineralization, while at the same time, hopefully, retaining their ability to inhibit bone resorption. (Tr. at 429:12-430:10 (Benedict Dir.); PTX 117).

234. Dr. Perkins was another P&G chemist, whom Dr. Benedict helped hire and who worked with Dr. Benedict on the bisphosphonate research for several years. (Tr. at 419:18-22 (Benedict Dir.)).

235. PTX 117 was prepared in the ordinary course of business and it was Dr. Benedict's ordinary course of business to prepare such research proposals for his supervisors. (Tr. at 430:11-17 (Benedict Dir.)).

236. A cyclic bisphosphonate is a bisphosphonate that has the geminal carbon atom incorporated into a five, six or seven member ring. (Tr. at 430:18-24 (Benedict Dir.)).

237. P&G made a large number of cyclic bisphosphonates, several of which it tested. The testing revealed that the cyclic bisphosphonates inhibited bone mineralization less than etidronate, but that they were not potent inhibitors of bone resorption, and therefore did not have a good therapeutic index. As a result, Dr. Benedict did not pursue cyclic bisphosphonates. (Tr. at 429:12-432:4 (Benedict Dir.)).

238. PTX 87 is an August 1, 1983 proposal by Dr. Benedict and Dr. Perkins to investigate new bisphosphonate compounds with a nitrogen atom in the structure. Dr. Benedict was aware that pamidronate, which is a hydroxy bisphosphonate with a terminal primary amino and alkyl chain, had good biological activity as an inhibitor of bone resorption. Dr. Benedict wanted to investigate the nitrogen atom in the molecule. Pamidronate is also called "APD." (Tr. at 432:9-24 (Benedict Dir.); PTX 87).

239. PTX 87 was prepared in the ordinary course of business and it was Dr. Benedict's ordinary course to prepare such proposals. (Tr. at 433:1-6 (Benedict Dir.)).

240. P&G made several compounds under the proposal reflected in PTX 87 and sent them for testing. Dr. Benedict found some of the compounds surprisingly potent, some not potent, and some very toxic. Dr. Benedict was unable to predict either the efficacy or the toxicity of the compounds without testing. (Tr. 433:21-435:7 (Benedict Dir.)).

241. PTX 531 is a biweekly report dated November 9, 1983 that Dr. Benedict prepared reporting on the synthesis and testing of a number of new pyridyl aminomethane bisphosphonates. PTX 531 was prepared in the ordinary course of business, and it was Dr. Benedict's ordinary course to prepare it. (Tr. at 435:8-436:12 (Benedict Dir.); PTX 531).

242. In PTX 531, Dr. Benedict stated:

> We are continuing our program of synthesis of new diphosphonates of the pyridyl aminomethane diphosphonate class. The purpose is, of course, to find the next generation diphosphonate. Along the way though, we have to "kiss a lot of frogs."

According to Dr. Benedict, his reference to "kiss a lot of frogs," meant that they had to make a lot of bisphosphonates and to test them in their models in order to find the best one. (Tr. at 436:13-437:16 (Benedict Dir.); PTX 531).

243. In addition, when discussing the results of the testing on one particular bisphosphonate, Dr. Benedict stated: "This was a surprise to me. It points out again how poorly we understand the structure/activity relationships among these compounds." According to Dr. Benedict, this was "an accurate confession of what we didn't know" at that time. (Tr. at 437:17-438:12 (Benedict Dir.); PTX 531).

244. PTX 86 is a report from Dr. Benedict dated January 16, 1984 concerning a class of aminomethane diphosphonates compounds that P&G had synthesized and tested.

The report discusses approximately two dozen compounds in this class that P&G had made at that time. All of these compounds were tested in one or more assays. (Tr. at 438:13-439:17 (Benedict Dir.)).

245. PTX 86 was prepared in the ordinary course of business, and it was Dr. Benedict's ordinary course to prepare it. (Tr. at 438:22-439:3 (Benedict Dir.)).

246. PTX 131 is a project proposal dated April 5, 1984 prepared by Dr. Benedict and Dr. Perkins. The research proposal was to create compounds in which the chain connecting the pyridyl ring to the geminal carbon would be an alkyl chain *i.e.*, contain a carbon atom, instead of a nitrogen atom. PTX 131 was prepared in the ordinary course of business, and it was Dr. Benedict's ordinary course to prepare it. (Tr. at 439:18-440:16 (Benedict Dir.)).

247. PTX 131 states, in pertinent part:

> It is uncertain that any of these substituted pyridyl ethane – 1,1-diphosphonates will be better therapeutic agents than the diphosphonates we already have prepared. Still, we feel it's very important that some of these compounds be prepared and evaluated in our in vitro and in vivo models for skeletal activity. P&G is the leader in this aspect of diphosphonate technology, but we can maintain our position only be constantly moving forward.

According to Dr. Benedict, the reference to uncertainties accurately reflected the science at that time. (Tr. at 440:17-441:17 (Benedict Dir.); PTX 131, PG77033).

248. Pursuant to this proposal, P&G made several members of the family of substituted pyridyl ethane diphosphonates and investigated them in various of the assays. (Tr. at 441:18-24 (Benedict Dir.)).

249. While Dr. Benedict worked at P&G, it was his practice and the practice of others at P&G to keep laboratory notebooks that carried records of the synthetic work

being performed and/or test evaluation models that were being run. Once a notebook was no longer in use, it would be returned to P&G's Central Records library for microfilming and permanent retention. Such laboratory notebooks were maintained in the ordinary course of business, and it was the ordinary course of P&G's business to keep such laboratory notebooks. (Tr. at 442:7-443:14 (Benedict Dir.)).

250. PTX 70 is a copy of one of Dr. Benedict's laboratory notebooks. PTX 70 covers the period of time from July 19, 1983 to June 28, 1985. This notebook shows the synthesis of almost one hundred bisphosphonate compounds during this time period. PTX 70 was kept by Dr. Benedict in the ordinary course of business, and it was his ordinary course to keep such laboratory notebooks. (Tr. at 442:1-6, 16-24; 443:1-6, 15-24 (Benedict Dir.); PTX 70).

251. PTX 69 is copy of Dr. Benedict's "idea book" in which he recorded ideas, thoughts, and concepts for new lines of research. Dr. Benedict kept PTX 69 in the ordinary course of business, and it was his ordinary course of business to record his ideas in such a book. (Tr. at 444:11-445:3 (Benedict Dir.); PTX 69).

252. PTX 69 covers the time period from February 18, 1983 to October 15, 1984. (Tr. at 445:4-7 (Benedict Dir.); PTX 69).

253. PTX 69 contains an entry dated November 2, 1983, which reflects Dr. Benedict's idea to make bisphosphonates that included vitamin B6-like structures. Vitamin B6 is a pyridyl-containing structure. Dr. Benedict wanted to see if it would be possible to incorporate these pyridyl-like rings into bisphosphonates. Dr. Perkins made some of these compounds. When P&G tested them, however, they learned that they were

not especially good inhibitors of bone resorption. (Tr. at 445:15-446:14 (Benedict Dir.); PTX 69 at PG 53832).

254. PTX 69 contains an entry dated November 3, 1983, which reflects Dr. Benedict's idea to remove one of the phosphonate groups of a bisphosphonate and replace it with a similar, but not identical carboxylated group, and to test whether the resulting compounds would have less affinity for the bone. In doing so, Dr. Benedict sought to address the bone binding affinity that was characteristic of known bisphosphonates, and that was believed to be related to the inhibition of bone mineralization. Dr. Benedict made and tested some of these compounds. However, the compounds did not bind sufficiently to bone in order to be good inhibitors of bone resorption. (Tr. at 446:15-448:3 (Benedict Dir.); PTX 69 at PG 53834).

255. PTX 69 contains an entry dated April 13, 1984, which reflects Dr. Benedict's idea to make new pyridyl bisphosphonates with more than one nitrogen atom in the pyridyl ring and to make modifications on the geminal carbon atom. Dr. Benedict's objective was to determine whether such modifications could affect the inhibition of bone mineralization while maintaining some of the beneficial aspects of inhibition of bone resorption. P&G made some of these compounds and found that, while they could impact inhibition of bone mineralization, the compounds were not especially good inhibitors of bone resorption. (Tr. at 448:4-449:9 (Benedict Dir.); PTX 69 at PG 53851).

256. PTX 69 contains an entry dated April 17, 1984, which shows Dr. Benedict's idea to make bisphosphonate compounds that contained sulfonamide moieties. P&G knew that sulfonamide drugs affected carbonic anhydrate enzymes, an important

enzyme in the osteoclast. Dr. Benedict hypothesized that bisphosphonate compounds containing sulfonamide moieties might effect the carbonic anhydrate enzyme cycle and might be effective inhibitors of bone resorption. Dr. Benedict made some of these compounds, but found that they did not work well at all. (Tr. at 449:10-450:16 (Benedict Dir.); PTX 69 at PG 53854).

257. PTX 69 contains an entry dated May 3, 1984, which shows Dr. Benedict's idea for a way to make hydroxyethane bisphosphonates ("EHDP") from ethane bisphosphonates ("EDP"). Dr. Benedict ultimately utilized this process to make 2-pyr EHDP in early March 1985. (Tr. at 450:17-452:19 (Benedict Dir.); PTX 69 at PG 53860).

258. PTX 69 contains a drawing of a generic structure that would also include risedronate (3-pyridyl EHDP) and 4-pyridyl EHDP, depending on the point of attachment to the pyridyl ring and if the R group was a hydrogen. (Tr. at 453:1-12 (Benedict Dir.); PTX 69 at PG 53860).

259. As of May 3, 1984, although Dr. Benedict had a concept that 2-pyr EHDP, risedronate), and 4-pyr EHDP would have "some activity," he could not have predicted with certainty how efficacious or how toxic these compounds would be. (Tr. at 453:13-23 (Benedict Dir.)).

260. PTX 69 contains an entry dated June 19, 1984, which reflects Dr. Benedict's idea to modify the linking chain between the head group of a bisphosphonate and the pyridine ring by incorporating an oxygen atom in the chain, instead of a nitrogen atom or a carbon atom. Dr. Benedict made some of these compounds, but found that they were not as good at inhibiting bone resorption as bisphosphonates containing a nitrogen

atom or a carbon atom in the chain. (Tr. at 453:24-454:22 (Benedict Dir.); PTX 69 at PG 53868).

261. Prior to 1985, P&G had identified two primary bisphosphonates as candidates for development: 2-pyridyl ethane diphosphonate ("2-pyr EDP") and 3-picolyl aminomethane diphosphonate ("3-pic AMDP"). 3-pic AMDP was dropped from further development early on because of toxicity issues. 2-pyr EDP went into early Phase I testing for FDA purposes. (Tr. at 454:23-456:10 (Benedict Dir.)).

262. PTX 72 is a copy of one of Dr. Benedict's lab notebooks for the time period August 5, 1981 to June 1985. Dr. Benedict kept PTX 72 in the ordinary course of business, and it was his ordinary course of his business to keep such lab notebooks. (Tr. at 456:11-457:1 (Benedict Dir.)).

263. PTX 72 shows Dr. Benedict's synthesis of 2-(2-pyridyl)-1-hydroxyethane diphosphonic acid ("2-pyr EHDP") on March 11, 1985. (Tr. at 457:2-10 (Benedict Dir.); PTX 72 at PG 54501).

264. Dr. Benedict was the first person to make 2-pyr EHDP. He made 2-pyr EHDP on March 11, 1985. (Tr. at 457:14-16 (Benedict Dir.))

265. After Dr. Benedict made 2-pyr EHDP, he sent it for various types of testing, including a crystal growth inhibition test, the Schenk assay, and the TPTX assay. (Tr. at 457:17-22)

266. PTX 109 is a biweekly report that Dr. Benedict dated April 8, 1985, summarizing the results of the TPTX testing on the 2-pyr EHDP compound. In the report, Dr. Benedict stated:

> The recent assessment of 2-pyridyl EHDP (Figure 1) by K.Y. Johnson in her TPTX model indicates that this

> hydroxyl diphosphonate is approximately 10X more active than its nonhydroxy counterpart, 2-pyridyl EDP (Figure 2).

(Tr. at 459:4-12 (Benedict Dir.); PTX 109).

267. At the time Dr. Benedict made 2-pyr EHDP, he would not have been able to predict the difference in efficacy between 2-pyr EHDP and 2-pyr EDP. (Tr. at 459:17-20 (Benedict Dir.); PTX 109).

268. PTX 507 is a biweekly report written by Jim Powell, another member of the research group to which Dr. Benedict belonged, dated May 22, 1985. Dr. Benedict would have received this report while he worked at P&G. Mr. Powell prepared the report in the ordinary course of business, and Dr. Benedict received it in the ordinary course of business. (Tr. at 459:21-460:20 (Benedict Dir.)).

269. In PTX 507, Mr. Powell wrote:

> The first test of the hypothesis was a study in the Schenk model (J. Bevan) of a 2-pyridyl analogue having a hydroxyl substitution on the geminal carbon. This compound, having greater affinity for hydroxyapatite than the parent drug, was significantly more toxic to soft tissue in this model."

Thus, when the animals were dosed with the 2-pyr EHDP compound, at the injection site, there was some soft tissue necrosis that was probably predictive of other toxicity. (Tr. at 460:21-461:17 (Benedict Dir.); PTX 507).

270. At the time that Dr. Benedict made 2-pyr EHDP, he continued to make other compounds, including a 3-(3-pyridyl)-1-hydroxypropane-1,1-diphosphonate ("3-pyr PHDP"). Dr. Benedict made 3-pyr PHDP in order to determine the result of modifying the chain length and the position of the nitrogen on the ring. P&G evaluated this compound in the crystal growth inhibition assay and the TPTX model. Dr. Benedict

was surprised and disappointed to find from these tests that 3-pyr PHDP was hardly active in inhibiting bone formation. (Tr. at 465:15-467:4 (Benedict Dir.)).

271. As noted by Dr. Lenz, 3-pyr PHDP was reported in a P&G document as having "no activity even at the highest does tested of 1.0 mg P/kg." (Tr. 219:19-220:14 (Lenz Cross); PTX 138.)

272. PTX 67 is a copy of one of Dr. Benedict's lab notebooks, covering the time period from January 25, 1985 to June 28, 1985. PTX 67 was kept by Dr. Benedict in the ordinary course of business, and it was his ordinary course to keep such laboratory notebooks. (Tr. at 464:14-465:8 (Benedict Dir.); PTX 67).

273. PTX 67 reflects the synthesis of 3-pyr PHDP by Dr. Benedict on April 26, 1985. (Tr. at 465:9-466:1-2 (Benedict Dir.); PTX 67at PG 53518-53520).

274. PTX 67 reflects Dr. Benedict's first synthesis, of 3-pyridyl EHDP (*i.e.* risedronate), on May 3, 1985. (Tr. at 420:19-421:1, 467:5-22 (Benedict Dir.); PTX 67 at PG 53521-53522).

275. NE-58019 is the compound number P&G used to refer to risedronate during its developments. (Tr. at 729:7-8 (McOsker Dir.)).

1. Dr. Benedict's Diligence in Reduction to Practice of Claims 4, 16, and 23 of the '122 Patent

276. Once Dr. Benedict had made risedronate, on May 31, 1985, he analyzed the compound to confirm its purity and to determine its specific activity. (Tr. at 468:15-19 (Benedict Dir.)). In particular, PTX 70 reflects the titration of risedronate to determine its specific activity. (Tr. at 468:20-469:15 (Benedict Dir.); PTX 70 at PG 54042-54043).

277. Shortly after titration analysis, Dr. Benedict sent risedronate to the University of Arizona for TPTX testing on June 3, 1985. (Tr. at 468:8-11, 469:16-20 (Benedict Dir.); PTX 67 at PG 53522).

278. PTX 137 is a biweekly report by Dr. Benedict dated July 26, 1985. PTX 137 was prepared by Dr. Benedict in the ordinary course of business, and it was his ordinary course to prepare such reports. (Tr. at 471:12-472:11 (Benedict Dir.); PTX 137.

279. PTX 137 and PTX 138 report on the syntheses of larger quantities of hydroxyalkane diphosphonates (including 2-pyr EHDP, 3-pyr EHDP, and 4-pyr EHDP), and PTX 137 additionally reports the testing of two bisphosphonates, risedronate and 3-pyr-PHDP. Referring to risedronate, (3-pyr EHDP) PTX137 states: "Not surprisingly 2-(3-pyridyl)-1-hydroxyethane-1,1-bis(phosphonate) (1b) was active at the lowest dose evaluated, 0.01 mg P/kg." (Tr. at 471:18-472:23 (Benedict Dir.); PTX 137; PTX 138).

280. Referring to 3-pyr PHDP, PTX 137 states: "Surprisingly, compound 1e, 3-(3-pyridyl)-1-hydroxypropane-1,1 bis(phosphonate) showed no activity even at the highest dose tested which was 1.0 mg P/kg. Its hard to believe that one extra methylene group could make such a difference, but . . . ." (Tr. at 473:12-19 (Benedict Dir.); PTX 137).

281. The purpose of the study reflected in PTX 137 was to put evaluation of 3-pyr PHDP into perspective with risedronate, in order to determine the effect of lengthening the chain by one carbon atom. Dr. Benedict hoped that this modification would provide an even better response than they had obtained with risedronate. So, P&G tested risedronate at a fairly high dose (0.01 mg P/kg), at which Dr. Benedict was not surprised to see that risedronate showed activity. However, for the 3-pyr PHDP

compound, "amazingly, the response dropped to virtually nothing." Instead of improving the response, as Dr. Benedict had hoped, adding one carbon atom to the chain resulted in a compound that was almost 100 times less potent than risedronate. (Tr. at 472:24-474:6 (Benedict Dir.); PTX 137).

282. Dr. Benedict continued to make additional bisphosphonate compounds even after he made risedronate, including 2-(4-pyridyl)-1-hydroxyethane-1,1-bisphosphonate ("4-pyr EHDP"). (Tr. at 480:15-481:18 (Benedict Dir.); PTX 67).

283. PTX 67 reflects the synthesis by Dr. Benedict of 4-pyr EHDP on May 8, 1985. (Tr. at 480:21; 491:16 (Benedict Dir.); PTX 67 at PG 53525).

B. P&G's Testing of Risedronate and Related Compounds

284. After Dr. Benedict made the 2-pyr EHDP, 3-pyr EHDP, and 4-pyr EHDP compounds, he submitted them for efficacy and toxicity screening. (Tr. at 457:17-461:17, 468:8-469, 481:2-20 (Benedict Dir.)).

285. Screening assays were developed and used to make a first cut in a short timeframe on a large number of compounds tested and to identify initially which compounds had potential in terms of an efficacious and safe application in a human. (Tr. at 839:3-15 (Miller Dir.)).

1. Efficacy Screening

286. The screening assays used to test the efficacy of bisphosphonates for the potential treatment of osteoporosis in the mid-1980s were the Schenk (growing rat) assay and the thyroidparathyroidectomized rat model ("TPTX") assay. P&G utilized these assays in its bisphosphonate screening program. (Tr. at 714:20-715:11 (McOsker Dir.); Tr. at 840:22-841:8 (Miller Dir.)).

287. The Schenk and TPTX assays were highly regarded in the field in the mid-1980s and are, in fact, still highly regarded today. (Tr. at 841:11-13 (Miller Dir.)).

288. It is desirable to find compounds that are the most effective at the lowest dose – *i.e.*, the most potent drugs. (Tr. at 849:10-14 (Miller Dir.)).

289. The purpose of these assays was to screen new bisphosphonate compounds to gauge their antiresorptive potency. (Tr. at 715:7-715:11 (McOsker Dir.)). P&G sought to use these assays to identify compounds that had the greatest antiresorptive activity with the least inhibition of bone mineralization. (Tr. at 720:5-24 (McOsker Dir.)).

290. Various individuals at P&G conducted the TPTX and Schenk assays, including Jocelyn McOsker, Karen Johnson, and John Bevan. (Tr. at 458:5-9, 502:22-503:9 (Benedict Dir.); Tr. at 718:15-18, 740:20-741:12, 741:23-742:19 (McOsker Dir.)).

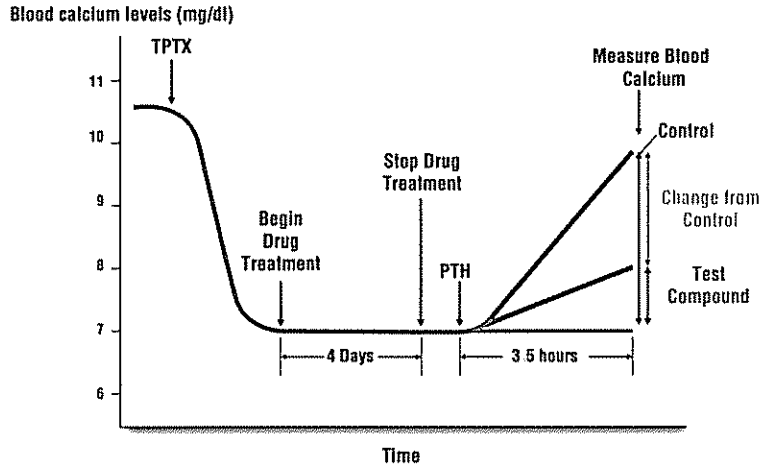
a. TPTX Assay

291. The TPTX assay involves the use of rats that have had their thyroid and parathyroid glands removed. The parathyroid gland secretes parathyroid hormone, which causes calcium to be released from bone into the bloodstream and thereby regulates the level of blood calcium. When the parathyroid gland and its parathyroid hormone are removed, blood calcium levels drop. In the TPTX assay, after removal of their thyroid and parathyroid glands and reduction in their blood calcium levels, rats are dosed with compounds for a period of four days. They are then given an injection of parathyroid hormone, which ordinarily would stimulate an increase in the level of blood calcium. If a test compound is effective in inhibiting bone resorption, rats dosed with that compound will see a smaller increase in blood calcium levels compared to a control because the antiresorptive compound blocks the release of calcium from the bone. The antiresorptive

effect of test compounds can be observed by measuring the difference in increases of blood calcium level from the control. (Tr. at 845:19-848:5 (Miller Dir.); Tr. at 718:19-719:9 (McOsker Dir.); PTX 22 at PG 23093-23095; P-38).

292. PTX 22 is a report summarizing the results of the Schenk and TPTX assays for risedronate written by Ms. McOsker. It was Ms. McOsker's usual practice to prepare such reports in connection with the efficacy screening that she conducted, and such reports were maintained by P&G in the ordinary course of business. (Tr. 733:1-734:21 (McOsker Direct).)

293. The picture below illustrates the methodology of the TPTX assay:



(Tr. at 845:18-848:5 (Miller Dir.); Slide P-38).

294. The TPTX assay is straightforward to administer. (Tr. at 721:22-7:22-1 (McOsker Dir.)).

295. The results of the TPTX assay are expressed as a lowest effective dose ("LED"), which indicates the lowest dose at which a test compound inhibits bone resorption. (Tr. at 848:9-12 (Miller Dir.); Tr. at 719:16-18 (McOsker Dir.)). Sometimes,

the results would be reported as the "lowest effective dose tested" or "LEDT," if the compound was active at the lowest dose tested. (Tr. at 718:6-14 (McOsker Dir.)).

296. The LED information from the TPTX assay informs researchers as to whether a compound is effective at inhibiting bone resorption and how potent the compound is. (Tr. at 849:2-14 (Miller Dir.)).

297. The TPTX assay has proven very reliable in predicting efficacy of compounds ultimately used in humans. (Tr. at 848:13-21 (Miller Dir.)).

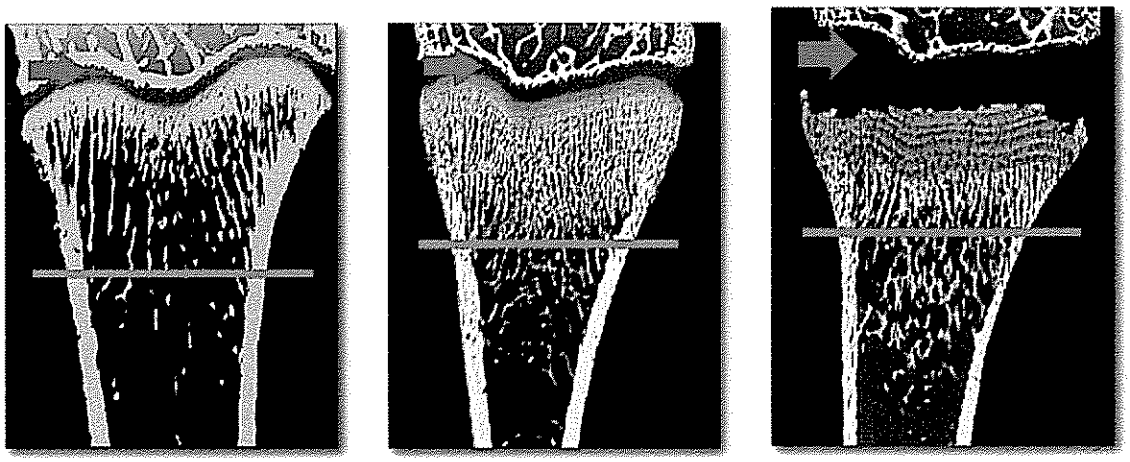
298. Jocelyn McOsker began conducting the TPTX assay at P&G in May 1985, and continued to conduct animal model screening for new bisphosphonate compounds for several years thereafter. (Tr. at 712:17-713:16, 721:7-722:11 (McOsker Dir.)). When she joined P&G, Ms. McOsker received two weeks of intensive training learning the procedures associated with these assays. (Tr. at 721:13-21 (McOsker Dir.)). Subsequently, she conducted the TPTX assay many times. (Tr. at 722:7-11 (McOsker Dir.)).

b. Schenk Assay

299. The Schenk assay, which was developed in the 1970s, involves the use of growing rats and examination of the effects of test compounds on bone formation. Normally, new bone forms gradually at the end of the growth plate, analogous to adding height to a wall by adding bricks, thus extending the length of the bone. In the Schenk assay, rats are treated with a test compound for a period of seven days. If the test compound is effective at inhibiting bone resorption, it will prevent the normal resorption that happens as part of bone growth, and there will be a larger accumulation of newly-formed bone near the growth plate (as compared to a control). In addition, if a test compound inhibits bone mineralization, a widening of the growth plate will be observed.

At the end of the dosing period, the animals are sacrificed and the bones are removed and analyzed to determine the extent to which the test compound inhibited bone resorption and/or bone mineralization. (Tr. at 841:14-844:7 (Miller Dir.); Tr. at 715:12-22, 716:10-717:2 (McOsker Dir.); P-37).

300. The picture below illustrates the methodology of the Schenk assay.



(Tr. at 842:12-844:7 (Miller Dir.); Slide P-37).

301. The results of the Schenk assay are expressed as a "lowest effective dose" or "LED," which indicates the lowest dose at which a test compound inhibits bone resorption. (Tr. at 844:10-24 (Miller Dir.); Tr. at 718:1-5 (McOsker Dir.)).

302. The Schenk assay has proven very reliable in predicting the efficacy of compounds ultimately used in humans. (Tr. at 845:1-10 (Miller Dir.)).

303. In the mid-1980s, there were two available methods to measure the accumulation of bone in the Schenk assay: bone densitometry using single photon absorptiometry ("SPA") and histomorphometry. (Tr. at 855:8-856:1 (Miller Dir.); Tr. at 716:16-717:2 (McOsker Dir.)).

304. In the SPA technique, the bone is put into a machine that passes high-energy photons through the bone. By measuring how much of the photon emission is absorbed, SPA indicates the overall bone density and enables one to determine whether there is an increase in bone mass. (Tr. at 855:8-856:1 (Miller Dir.); Tr. at 716:19-717:17 (McOsker Dir.)).

305. Histomorphometry involves quantifying of bone vs. non-bone "volume" from a cross section of bone sample. (Tr. at 855:8-856:1 (Miller Dir.); Tr. at 716:19-717:7 (McOsker Dir.)).

306. Histomorphometry also indicates whether there was an effect on the mineralization of the bone. (Tr. at 717:21-24 (McOsker Dir.)).

307. Both Schenk assay methods accurately indicate whether there was antiresorptive activity. (Tr. at 717:18-21 (McOsker Dir.); Tr. at 758:23-759:13 (McOsker Cross)).

c. Efficacy Screening of Risedronate

308. The first TPTX assay on risedronate was conducted at the University of Arizona. (Tr. at 725:5-20 (McOsker Dir.)). That test indicated that risedronate had antiresorptive activity at the lowest dose tested of 0.01 mg P/kg/day. (Tr. at 749:20-750:5 (McOsker Cross)).

309. In order to determine whether risedronate was potent at an even lower dose, P&G subjected risedronate to a follow-up TPTX assay in-house. (Tr. at 725:5-20 (McOsker Dir.)). Ms. McOsker supervised this testing, which was conducted from September 23-September 27, 1985. (Tr. at 725:21-23 (McOsker Dir.); PTX 514).

310. PTX 514 is Ms. McOsker's lab notebook reflecting TPTX testing conducted on risedronate by Ms. McOsker from September 11-25, 1985. It was Ms.

McOsker's usual practice to maintain such lab notebooks in connection with the laboratory work that she conducted, and such lab notebooks were maintained by P&G in the ordinary course of business. (Tr. 722:12-723:5 (McOsker Direct); Tr. 443:4-14 (Benedict Direct).)

311. Given the results of the initial TPTX assay, P&G decided to re-test risedronate at doses of 0.1, 0.01, 0.001, and 0.0003 mg P/kg/day. PTX 514 at PG 191298. Risedronate showed anti-resorptive activity at all of these doses. (Tr. at 725:24-726:3 (McOsker Dir.)).

312. As a result of this second TPTX test, P&G determined that risedronate had a LEDT of 0.0003 mg P/kg/day. (Tr. at 726:4-10 (McOsker Dir.); PTX 22 at PG 23092; PTX 141).

313. PTX 141 is a bi-weekly report written by Ms. McOsker dated October 18, 1985 that discusses the TPTX testing results for risedronate. Such reports were made in the ordinary course of business and were distributed across the pharmaceutical division to share information. (Tr. 728:8-729:12 (McOsker Direct).)

314. This result was surprising to Ms. McOsker because, in a screening assay, one expects to see a dose response curve ranging from an effective dose to an ineffective dose. (Tr. at 726:11-21 (McOsker Dir.)). However, in the case of risedronate, it was active at all of the doses tested. (*Id.*)

315. Given the surprising nature of the results, Ms. McOsker's initial reaction was that she might have made an error in performing the test. (Tr. at 752:11-16 (McOsker Cross)). To ensure this was not the case, she verified that the dosing solutions

had been prepared properly and that the calculations were correct. She concluded that the results were accurate. (Tr. at 726:22-727:5 (McOsker Dir.)).

316. Immediately upon seeing these results, Ms. McOsker went to see Dr. Benedict and shared the results with him. (Tr. at 727:6-11 (McOsker Dir.)). When Ms. McOsker told Dr. Benedict the outcome of the second TPTX test, he was "amazed" by the results. (Tr. at 727:12-17 (McOsker Dir.)).

317. Subsequently, P&G also tested risedronate in the Schenk assay. (Tr. at 730:6-11 (McOsker Dir.)). Ms. McOsker also supervised this test, which was conducted from April 8, 1986 to April 14, 1986. (Tr. at 730:12-17 (McOsker Dir.); PTX 519 at PG 191470-73).

318. PTX 519 is a lab notebook witnessed by Ms. McOsker reflecting Schenk testing that was conducted on risedronate. Such lab notebooks were maintained by P&G in the ordinary course of business. (Tr. 730:18-731:15 (McOsker Direct); Tr. 443:4-14 (Benedict Direct).)

319. P&G tested risedronate in the Schenk assay at doses of 1.0, 0.01, 0.001, and 0.0003 mg P/kg/day. (Tr. at 732:11-13 (McOsker Dir.); PTX 519 at PG 191452).

320. After the animals used in the assay were sacrificed, P&G analyzed the bones using both SPA and histomorphometry. Both methodologies indicated that risedronate showed antiresorptive activity at the lowest dose tested of 0.0003 mg P/kg/day, although the increase in bone volume at the 0.0003 mg P/kg/day dose was more noticeable based on the SPA analysis. Even with histomorphological analysis, P&G saw over a 29% increase in bone volume from control at the 0.0003 mg P/kg/day dose. P&G concluded that this increase was not statistically significant based on application of a very